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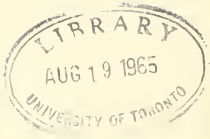
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SAMUEL BROCK, M.D., AND WILLARD E. KAY, M.D.

NEW YORK

SAN FRANCISCO

In a series of cases studied at the U. S. Army General Hospital No. 41, Fox Hills, Staten Island, N. Y., over a period of five months, such interesting manifestations were noted from an endocrinologic and myopathic standpoint, that their publication seems warranted.

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*CASE 1.—An advanced instance of polyglandular disturbance, characterized by a dystrophia adiposo-genitalis, precipitated by influenza, associated with a muscular dystrophy, and unusual reactions of the vegetative nervous system. A consideration of the endocrine balance and the metabolism findings is of unusual interest.*

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In March, 1919, he again entered the hospital where he remained until about May 1. These symptoms progressed, and, in addition, he noted a frequency of urination. In the beginning of the illness he lost about twenty pounds of

weight; then there followed an increase in weight which has continued ever since, until now he weighs 240 pounds.

In July, 1919, he was sent back to the United States. About this time, in addition to the definite progression of the other symptoms noted, a craving for sweets and a loss of erections, libido and ejaculatory reflex became evident; although prior to this time he was quite virile, there have since been but few erections or feelings of sexual desire. A change of voice (its pitch becoming raised) began at this time.

He has also noticed that his upper extremities have grown in length. An increased thirst has developed in the past few weeks.

Gastro-Intestinal: His appetite is rather capricious. Bowels: Normal. Vomiting: Of considerable frequency in the past six months. It is unassociated with abdominal pain or hematemesis. A "sour stomach" with gaseous



Fig. 1 (Case 1).—Dystrophia adiposogenitalis.

and acid eructations accompanies this symptom, together with a sense of fullness in the abdomen. There is no relation to the intake of food; the vomiting is aggravated by the acid eructations and alleviated by an empty stomach.

Genito-Urinary: No dysuria or hematuria. The sexual deficiencies have been mentioned. No history of enuresis.

Respiratory: No cough; no hemoptysis. Sharp and stabbing pain occurs in the right lower chest, at times. No history of epistaxis.

Cardiovascular: A considerable degree of shortness of breath is present. There is edema of the legs when he is up and about. Dizziness and a tendency toward syncope are likewise noted.

Central Nervous System: Headache is an insignificant symptom seldom complained of, and when present, is vertical in type. No complaints in the spheres of vision or hearing. A certain amount of emotional instability is complained of, manifested by his getting upset more easily than heretofore.

Skin: Shaving was begun at the age of 17 and resorted to once or twice a week until about a year ago. Since that time, the period between shav-

ings has increased considerably, until now it is hardly necessary. Many attacks of urticaria have occurred in the last few years.

*Neurologic and General Physical Examination.*—NEUROLOGIC: 1. Cranial nerves negative: Pupils equal, react fairly well to light and accommodation; they are fairly round in contour. The fundi and the fields of vision display no abnormality; no hemianopsia.

3. Reflexes: Knee jerks, right much diminished, left absent. Achilles tendon jerk, left much diminished, right absent. No Babinski, Oppenheim or no past-pointing.

2. Cerebellar functions: No adiadokokinesia; no manual or pedal ataxia; Chaddock phenomena; no ankle clonus. The middle and lower abdominal reflexes are present. The cremasteric reflexes are not always elicited; when they are, a diminution is noted.

4. Motor: Motor power is well preserved in the upper extremities. The muscles of the thigh, viz., quadriceps extensors, hamstrings, abductors and the glutei are considerably weakened, especially the abductors, the hamstrings, and the flexors of the thigh (pelfofemoral) are involved, whereas the inverters, evertors, flexors and extensors of the feet are fairly powerful. This stands in direct contrast to the fact that the legs are much thinner than the thighs (pseudohypertrophy of thighs?).



Fig. 2 (Case 1).—The genitalia.

*Electrical Examination.*—Examination was confined to three muscles on the left side, the tibialis anticus, gastrocnemius and quadriceps extensor. Faradic response was obtained in all three muscles; but it was weak and appeared only when the primary coil was completely covered. A quick galvanic response, without tetanus or reversal, was obtained from all three muscles; but the reaction did not start to appear until the current reached 15 milliamperes.

Examination with the Jones' condensor: A barely perceptible response was obtained with the following strength in microfarads, using 100 volts: Tibialis anticus, 0.02; gastrocnemius, 0.08; quadriceps extensor, 0.07.

In the control, a normal person, a response was obtained with 0.01 microfarad in all three muscles.

**SUMMARY:** Marked diminution of faradic and galvanic irritability. The reaction of degeneration is not present. A waddling gait is present, associated with lumbar lordosis.

*Sensory:* The appreciation of all forms of sensation seems slightly diminished on the left side, with the exception of the muscles and joint sense which seems to be well preserved on both sides. The sensory findings vary, and areas of anesthesia (touch) are found on the dorsum of the feet; pain appreciation,

heat and cold perception, however, are well preserved. Vibration sense is lost in both lower extremities. The sensory abnormalities disclosed are inconstant, and are definitely of a functional nature. Reexamination at intervals of months reveals no essential change in the sensory sphere.

6. Psychiatric examination reveals no abnormalities. The patient is neither depressed nor taciturn.

*General Physical Examination.*—The figure is of a feminine type. Deposits of fat are especially noted over the iliac regions and the buttocks, in the pubic region and on the lower abdomen. A collar of fat in the neck obscures the thyroid cartilages (pomum Adami); a questionable enlargement of the thyroid gland is present. Special deposits were noted on the outer aspects of both thighs and in the breasts. The breasts are notably large, the right being larger than the left (Fig. 1).

The skin is quite smooth, soft, pinkish and dry; its thinness, as determined by the hypodermic needle, deserves special mention. The skin is quite easily bruised. The face is beardless; the hair is dry and stiff. The configuration of the genital hairs is distinctly of a feminine type (Fig. 1) the hair in this region and in the axilla being quite sparse.

The testicles are quite small and atrophic; the scrotal folds surround the penis, like labia, being inserted laterally to the penis (Fig. 2).



Fig. 3 (Case 1).—The teeth.

The teeth are small; abnormal spacing is noted between the incisors; especially the lower central incisors. The upper central incisors are rather large. The canines simulate the incisors, and lack the fang form (Fig. 3).

The hands are large, but not unusually so.

With the exception of the bilateral genu recurvatum and genu valgum, and the marked lumbar lordosis, hyperextensibility is not found in any other joints.

*Nose and Throat:* Aside from deflection of the nasal septum to the right, no other nasal abnormalities found. The tonsils are moderately large; the pharynx is negative.

*Ears:* The ears reveal normal hearing, and are normal to labyrinthine (Bárány) tests.

*Eyes:* The pupils are usually dilated and react well to light and accommodation; on convergence, the left eye quite constantly fails (i. e., swings outward). Vision: Oct. 14, 1919, right, 20/30 plus; left, 20/30 plus; 1 degree esophoria. Ocular movements good in all directions. Fields show no defects in either eye. Outside of very slight blurring in the left disk margins, both fundi are negative. Conclusions: No ocular abnormalities noted. Feb. 9, 1920, vision was, right, 20/20; left, 20/20. No change since above examination. March 1 and March 20, 1920, perimetric examination to form and color was normal. June 5: Fundi and perimetric examination to form and color were normal.

*Lungs:* Normal.

Heart: The point of maximum intensity is not seen. The left border is 0.5 cm. outside the left nipple line; at the apex the first sound is heard rather weakly; a soft systolic murmur is heard at the apex, but it is not transmitted. The action of tryamin reveals a normal cardiac response.

Blood Pressure: Taken at intervals of two minutes.

Pulse	Blood Pressure	
	Systolic	Diastolic
90	122	80
90	122	82
90	120	85
94	120	84
90	122	85
90	122	84
94	122	84



Fig. 4 (Case 1).—Roentgenogram of the sella turcica.

When taken at intervals of one minute, the blood pressure was:

Systolic	Diastolic
122	85
122	85
122	84

Aside from a slight increase in the pulse rate, no other abnormalities are found.

Cyanosis is not noted in hands or feet. Edema of a moderate degree is found in the lower extremities, more especially after exertion.

Abdomen: No viscera are palpable. The markedly adipose pendulous abdominal wall has been mentioned; numerous striae are seen here as well as over the thigh. Rectal examination reveals an unusually small, firm prostate.

Glands: No special adenopathy.

Temperature: Records taken daily, every hour or two, for three weeks show a range between 98 F. in the morning and 99.4 F. in the afternoon. The afternoon and evening rise are quite constant.

## LABORATORY DATA

	Feb. 9, 1920	Feb. 22, 1920	May, 1920
Erythrocytes	4,100,000	5,400,000	
Leukocytes	8,200	9,200	7,600
Hemoglobin, per cent.	85	90	80
Differential Count:			
Small mononuclears, per cent.	14	20	16
Large mononuclears, per cent.	10	3	12
Polymorphonuclears, per cent.	76	77	72

## BLOOD CHEMISTRY \*

Blood sugar (fasting stomach, March, 1920), 0.058 per cent.		
Blood sugar curve (May, 1920)	Blood Per Cent.	Urine.
Fasting	0.078	None
One hour after taking 183.5 gm. glucose.	0.140	None
Two hours afterward.	0.104	None
Blood sugar curve (August, 1920): Determined four months later when the patient was gaining weight rapidly, having attained 250 pounds.		
	Per Cent.	
Fasting	0.133	
One half hour after taking 183.5 gm. of glucose.	0.238	
Two hours afterward.	0.312	
Three hours afterward.	0.232	

(\* These determinations were made in the laboratory of Dr. George Draper.)

Urea nitrogen: 15.4 mg. per 100 c.c. of blood (May, 1920).

Blood creatinin: 1.97 mg. per 100 c.c. of blood (March, 1920).

Blood creatinin: 1.4 mg. per 100 c.c. of blood (May, 1920).

Blood creatin: 4.1 mg. per 100 c.c. of blood (May, 1920).

Blood uric acids: 2.3 mg. per 100 c.c. of blood (May, 1920).

Blood calcium: 11.7 mg. per 100 c.c. of blood (April, 1920).

Blood carbon dioxide: 62.4 volume per cent.

Blood Wassermann reaction was negative Oct. 17, 1919, and Feb. 10, 1920.

Bleeding time: 2 minutes.

Coagulation time:  $4\frac{1}{2}$  minutes.

## FECES

March 1, 1920: Mucus, negative; muscle fibers, few striated and nonstriated fibers present; fat, moderate; starch, negative.

March 3, 1920: After the ingestion of 200 gm. fat in the form of butter, the color was dark brown; consistence, hard; mucus, negative; blood, free (occult), negative; muscle fiber, none; fat, moderate amount; no appreciable increase of this substance over that found on previous examination; starch, negative.

## STOMACH CONTENTS

Oct. 21, 1919	March 5, 1920
Free hydrochloric acid, negative	27
Occult blood, negative	Negative
Total acidity	59

## SPINAL FLUID

Pressure, normal; transparency, clear; cell count two; globulin, negative; Wassermann, negative; colloidal gold curve, normal for preliminary and final curves.

## URINE

Numerous urine examinations were made at varying intervals. They all revealed:

Amber color; clear; acid; specific gravity varying between 1.010 and 1.030, with an average of about 1.022; albumin, negative; sugar negative; acetone, negative. Casts were not found at any time. The average output of eight twenty-four-hour observations was 1,300 c.c. with a range of from 750 to 1,900 c.c. Phenolphthalein showed 25 per cent. output for the first hour; 40 per cent. for the second hour; total, 65 per cent. Total nitrogen, 11.7 gm.; uric acid, 0.47 gm.; urinary creatin, 0.09 gm.; urinary creatinin, 1.4 gm.

*Sugar Tolerance Test* (Alimentary Glycosuria).—No glycosuria after 100 gm. glucose, after 183 gm. glucose, after 100 gm. glucose with 1 c.c. of 1:1,000 epinephrin solution, hypodermically, nor after 150 gm. glucose with 1 c.c. of 1:1,000 epinephrin, hypodermically.



*Pathology.*—A specimen of muscle removed from the biceps of the right thigh showed on gross examination a distinct pallor. Histologic examination "does not appear to show any pathologic change of importance. There is some fatty infiltration, but the muscle bundles themselves do not exhibit any evidence of degeneration or other lesion of significance." (Dr. K. M. Vogel.) These findings indicate very strongly the early stages of muscle dystrophy.

#### ROENTGEN-RAY FINDINGS

*Chest.*—Aug. 12, 1919: Apices clear. Moderate amount of peribronchial infiltration on both sides, especially right base.

*Heart.*—Oct. 5, 1919: Transverse diameter of the heart shadow measures 14 cm. and does not show a definite enlargement, except in the regions of the auricles, and is the type of heart shadow noted in mitral insufficiency.

*Head.*—October 5: There is noted a deep sella turcica with rather long anterior clinoid process. No other irregularity or deformity noted in the bones of skull. (Fig. 4.)

February, 1920: Lateral stereo of head shows no evidence of pathology about sella turcica. The mastoids are clearly shown and are negative, as to bone pathology. Anteroposterior and lateral views show large frontal sinuses which are clear. Ethmoids and antra are clear. There is a shadow which appears to be a spur on right side of septum.

June 24, 1920: No further change in sella turcica is noted.

*Bones.*—March 2, 1920: The epiphyses of the lower end of tibia have united, but the epiphyseal line is still evident. This is seen in 90 per cent. of individuals of his age. All other joints taken are negative. A good portion of the shafts of the bones are shown, and also are negative.

*Stomach.*—March 2: Fluoroscopic examination shows the stomach normal in size and position. Peristalsis active and stomach begins emptying very quickly. Pylorus in midline; no filling defect noted in stomach. The duodenal bulb appears normal. Plate examination confirms fluoroscopic. There is no six-hour retention. The bowel has begun emptying in twenty-four hours and there is still some barium in large intestine in forty-eight hours. No abnormality is noted in the large intestine. Roentgen-ray findings are negative except for a hyperperistalsis in the stomach. Pineal shadow suggestive; thymus shadow absent.

#### MEASUREMENTS OF PATIENT

	Cm.
Total length .....	176.5
Circumference of head.....	57.5
Circumference of chest (at level of nipples) ..	101
Circumference of abdomen (at umbilicus).....	112.5
Sternoclavicular junction to anterior superior spine of ilium .....	39
Anterior superior spine to internal malleolus.....	93
Anterior superior spine to upper border of patella.....	48
Acromion to styloid process of radius.....	62.5
Acromion to tip of olecranon.....	34
Distance between acromion processes .....	42
Distance between iliac spines.....	25
Spanwidth .....	192
Penis .....	5.5
Testes .....	2.5 × 1
Thigh, right .....	63
Thigh, left .....	63
Calf, right .....	35
Calf, left .....	35.5
Arm, right .....	34
Arm, left .....	32.5
Torso-leg ratio .....	39/93 or 0.42

## EPINEPHRIN TEST (GOETSCH'S)

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Before administration . . . . .	96	122	90	
Epinephrin, 0.5 c.c., 1:1,000 solution, hypodermically:				
7 min. later . . . . .	104	136	88	Patient complains of nervousness. Has moderate tremor of hands.
10 min. later . . . . .	104	140	84	Tremor and throbbing of vessels and palpitation of heart marked. Patient feels nervous and "shaky."
16 min. later . . . . .	108	140	88	Tremor, palpitation and nervousness marked.
24 min. later . . . . .	108	142	88	Marked tremor, etc.
30 min. later . . . . .	102	145	100	Symptoms as above.
35 min. later . . . . .	104	150	95	Marked palpitation, tremor, nervousness, pallor. Respiration 22.
60 min. later . . . . .	112	165	90	Marked tremor, palpitation, throbbing of vessels. First sound at apex sharp with loud systolic murmur.
1 hr. and 30 min. later . . . . .	110	145	88	Tremor, palpitation, throbbing and nervousness marked.
2 hr. and 10 min. later . . . . .	120	135	88	Palpitation and throbbing of vessels still fairly marked. Patient still complains of nervousness.

## EPINEPHRIN TEST

	Pulse	Blood Pressure		Respiration	Symptoms and Signs
		Systolic	Diastolic		
Before administration . . . . .	82	112	90	24	
Epinephrin, 1 c.c., 1:1,000 solution, hypodermically:					
10 min. after . . . . .	100	148	85	29	"Feels nervous," the outstretched hands show considerable tremor; the face is somewhat blanched. Cardiac palpitation.
40 min. later . . . . .	100	140	80	35	Tremor marked; considerable cardiac palpitation, with pulsation of neck vessels. Definite pallor.

EPINEPHRIN TEST AND OBSERVATION OF SERGENT'S WHITE LINE  
(WHITE ADRENAL LINE)

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Before administration .....	80	120	80	
Epinephrin, 1 c.c., 1:1,000 solution, hypodermically:				
5 min. later.....	104	140	80	Tremor fairly marked. Heart thumping, palpitation marked, patient moderately pale, respiration rapid; pa- tient complains of feeling very nervous. <i>Disappear- ance of white adrenal line.</i>
10 min. later.....	112	140	80	<i>White adrenal line gradually reappearing, and becoming more marked.</i> Marked tremor, palpitation of heart, nervousness continuing.
15 min. later.....	112	145	80	<i>White adrenal line well marked, notwithstanding a maintenance of the height- ened blood pressure.</i> Tre- mor, etc., still marked.
25 min. later.....	115	140	80	<i>White adrenal line still marked. Blood pressure still high.</i>
30 min. later.....	112	135	78	White adrenal line still marked; blood pressure fall- ing; tremor, palpitation, nervousness, still present.

The interest in the above observations attaches to the rapid disappearance of the pure white adrenal line, as described by Sergeant, following the administration of epinephrin, and to its rapid reappearance in the face of the sustained increased blood pressure.

The length of time during which the blood pressure (systolic) remained elevated is quite unusual, as is also the persistence of the nervous and cardiac phenomena.

From the above observation it would seem that the presence of the white line depends on factors other than lowered blood pressure.

TYRAMIN AND OBSERVATIONS ON WHITE ADRENAL LINE

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Tyramin, 60 mg., hypodermically....	..	..	..	White adrenal line present.
5 min. later.....	80	140	78	White line just as marked as before drug's administra- tion.
10 min. later.....	80	145	80	Intensity of white line same.
15 min. later.....	64	130	80	Intensity of white line just as marked.

	Pulse	Blood Pressure		Respira- tion	Symptoms and Signs
		Systolic	Diastolic		
Before administration of 80 mg. tyramin, hypo- dermically .....	100	130	90	40	White line present
5 min. later.....	64	180	105	70	White line unchanged
10 min. later.....	68	186	104	78	White line unchanged
20 min. later.....	80	170	100	62	Temperature, 98.4 F.; white line unchanged

This again demonstrates the persistency of a marked line in the presence of an increased blood pressure, brought about by tyramin.

#### PITUITARY EXTRACT AND OBSERVATIONS ON WHITE ADRENAL LINE

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Pituitary extract, 1 c.c., hypodermi- cally, at 11 a. m.....				White adrenal line well marked.
5 min. later.....	..	...	..	White line has disappeared.
10 min. later.....	..	...	..	White line still not visible.
15 min. later.....	..	...	..	White line still not visible.
20 min. later.....	80	110	75	White line barely visible.
25 min. later.....	..	...	..	White line has appeared again faintly.
				Patient complains of cramps in abdomen, and desire to defecate. Defecation oc- curred.
Pituitary extract, 1 c.c., hypodermi- cally, at 2 p. m.				
1 min. later.....	..	...	..	White line present (xx).
2 min. later.....	..	...	..	White line present.
5 min. later.....	..	...	..	White line has disappeared.
10 min. later.....	84	110	70	White line has disappeared.
15 min. later.....	..	...	..	White line beginning to ap- pear. (Desire to defecate.) Patient complaining of cramps in abdomen.
20 min. later.....	..	...	..	White line faint.

#### PITUITRIN TEST

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Before administration pituitary ex- tract 1 c.c.....	84	120	90	
5 min. later.....	100 Small volume	120	90	Patient pale. Feels sleepy. Desire to defecate and urinate present. Cramps in abdomen.
10 min. later..	96 Small volume	120	90	
15 min. later.....	96 Small volume	120	90	Movement of bowels oc- curred.

## ATROPIN TEST

	Pulse	Blood Pressure		Respira- tion	Symptoms and Signs
		Systolic	Diastolic		
Before administration.....	80-84	122-126	80	16	
After administration $\frac{1}{4}$ gr., hypodermically, given at 9:15 p. m.					
9:25 p. m.....	68	112	70	22	Pupils dilating; dryness of mucous membrane beginning.
9:45 p. m.....	80	116	90	44	Considerable dryness of mouth, tongue and pharynx; pupils dilating further; feels hot; face flushed.
10:15 p. m.....	90	135	100	48	Marked dryness complained of, producing distress. Pupils widely dilated. Respiratory rate increasing further.
10:30 p. m.....	88	135	100	45	Same as 10:15 p. m.
10:45 p. m.....	96	135	90	90	Respiratory rate notably increased. Face flushed; skin and mucous membrane quite dry.
11:00 p. m.....	82	135	85	70	Mucous membrane of mouth not quite so dry; pupils still widely dilated.
11:15 p. m.....	80	135	90	38	Respiration less rapid; mucous membrane of mouth and pharynx not so dry. Face less flushed.

## PILOCARPIN TEST (1)

	Pulse	Blood Pressure		Respira- tion	Symptoms and Signs
		Systolic	Diastolic		
Before administration ..	100	120	90	28	Skin dry.
Administration of 0.008 gm., hypodermically:					
15 min. later.....	100	134	98	30	Moderate salivation; skin dry. A desire to defecate is present.
30 min. later.....	110	134	98	40	Moderate salivation; skin moderately moist.
45 min. later.....	110	130	95	50	Quite marked salivation and moisture of skin; axilla quite moist; temp. 98.6 F.
1 hour later ..	118	125	100	48	Salivation less marked. Skin less moist; desire to urinate present.

## PILOCARPIN TEST (2)

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Before administration .....	90	120	85	
Pilocarpin, 0.0065 gm., hypodermically:				
5 min. later.....	90	120	85	
10 min. later.....	96	120	80	Moderate salivation; slight sweating.
20 min. later.....	100	124	80	Quite marked salivation; moderate sweating, slight flushing of cheeks.
30 min. later.....	..	..	..	White line of Sergent well marked.
30 min. later.....	100	124	80	Rather marked salivation, skin moist. Patient urinated three times during action of the drug. Patient expectorated about three ounces of saliva.

## ERGOTIN TEST

	Pulse	Blood Pressure		Symptoms and Signs
		Systolic	Diastolic	
Before administration .....	84	124	80	
Ergotin, $\frac{1}{40}$ gr., hypodermically:				
5 min. later.....	88	122	80	
15 min. later.....	88	122	80	No special signs or symptoms noted.

## PHYSOSTIGMIN (ESERIN) TEST

	Pulse	Respiration	Symptoms and Signs
Before administration .....	92	34	
Physostigmin, $\frac{1}{50}$ grain:			
15 min. later.....	96	36	Outside of slight headache and slight salivation, no gastro-intestinal effects were noted during the hour following the giving of this drug. Blood pressure readings showed no change.

## ASCHNER'S PHENOMENON (OCULOCARDIAC REFLEX)

Pulse, 72; Slight increase to 84. Winking reflex, 13 per minute. Loewi's phenomenon (epinephrin instillation in conjunctival sac). Negative.

## GOETSCH'S SKIN TEST

This test was markedly positive. A large central area of blanching surrounded by a peripheral zone of reddening lasted from four to five hours. In the blanched area there was the characteristic goose flesh formation.

In view of the surprisingly high respiratory rates gotten in response to the injection of some of the foregoing drugs, it was decided to determine how much of a psychic factor entered into this peculiarity. Accordingly, 1 c.c. of sterile water was injected subcutaneously. Soon after the respiratory rate rose from 24 to 46. In view of this, the high respiratory rates recorded in the foregoing observations must be discounted considerably.

## CUSHING'S THERMO-REACTION

An attempt was made to determine the effect of pituitary extract injections on the temperature; injections were made on six successive occasions. A rise to 99.8 and 99.2 F. occurred on two occasions; the other four injections produced no reaction.

TABLE 1.—SYMPATHICOTONIA

	Case 1	Case 2	Case 3
1. Mydriasis.....	Positive	Positive	Negative
2. Paralysis of accommodation.....	Negative		Negative
3. Dryness of eyeball.....	Negative	Negative	Negative
4. Infrequency of winking.....	Negative	Positive (slight)	Positive
5. Dryness of mouth.....	Negative	Negative	Negative
6. Low gastric acidity.....	Negative	Negative	Negative
7. Increased gastric secretion.....	Positive	Negative	Negative
8. Lessened intestinal tonus.....	Negative	Negative	Positive ?
9. Constipation.....	Negative	Negative	Negative
10. Faulty convergence of eyes.....	Positive	Positive	Negative
11. Wide eyeslits.....	Positive	Negative	Negative
12. Exophthalmos.....	Negative	Negative	Negative
13. Tachycardia.....	Positive (slight)	Positive (slight)	Negative
14. High blood pressure.....	Slight	Positive (slight)	Negative
15. Vasoconstriction.....	Positive	Negative (slight)	Negative
16. Relaxation of detrusor of bladder (incontinence).....	Negative	Negative	Negative
17. Urticaria.....	Positive (history)	Negative	Negative
18. Atony of stomach.....	Negative	Positive	Positive
19. Gastropnoia.....	Negative	Positive	Negative
20. No dermatograpbia.....	Positive	Slight	Negative
21. Tonils small and atrophied.....	Negative	Positive	Negative
22. Gag reflex marked.....	Positive	Negative	Negative
23. Eosinopenia.....	Positive	Positive	Positive
24. Tachypnea with dyspnea not affected by atropin, i. e., rate not lowered by atropin.....	Positive	Negative	Negative
25. Dry hands and feet.....	Positive	Negative	Negative
26. Ashner's phenomenon (oculocardiac reflex) produces no change in pulse.....	Positive	Negative	Negative
27. Steatorrhea.....	Negative	Negative	Negative
28. Lowered carbohydrate tolerance before and after epinephrin administration.....	Negative	Negative	Negative
29. Pilocarpin causes no salivation.....	Negative	Positive	Negative
30. Loew's test positive.....	Negative	.....	Negative
31. Reaction to epinephrin.....	Positive (marked)	Negative	Negative
32. Pituitary extract.....	Fairly marked peripheral constriction; movement of bowels	.....	Same
33. Reaction to ergotin.....	Slight	.....	Slight
34. Tyramin.....	Marked reaction	.....	Slight reaction

## BASAL METABOLISM

1. March 27, 1920.—Calories per sq. meter per hour, 29.3. Variation, minus 26. per cent.<sup>1</sup>

2. April 15, 1920.—Calories per sq. meter per hour, 35.6. Variation minus 10 per cent.

Antuitrin (extract of anterior lobe of hypophysis, Parke, Davis & Co.) 1 c.c. was now given hypodermically; 15 minutes after the basal metabolism revealed: Calories per sq. meter per hour, 36.6. Variation, minus 7 per cent.; 45 minutes after: Calories per sq. meter per hour, 34.5. Variation, minus 13 per cent.

The patient was suffering from a rather severe rhinitis and pharyngitis, the temperature ranging from 99.5 to 100, while these determinations of April 15, 1920, were being obtained.

3. May 6, 1920.—Basal metabolism determinations with patient on 1 c.c. of antuitrin (Parke, Davis & Co.) by hypodermic, three times daily, for a period of two weeks, together with capsules of orchic extract, 5 grains, three times daily, revealed: Calories per sq. meter per hour, 33.7. Variation, minus 14.5 per cent.

1. Determination made by Dr. B. Sanger, department of metabolism, Presbyterian Hospital. The determinations of April 15 and May 6 were made by Dr. H. E. Marks, department of metabolism, College of Physicians and Surgeons (Columbia University).

## COMMENT

Owing to the patient's irregular respiratory excursion, the basal metabolism findings were obtained with difficulty. Such variations, as may be ascribed to respiratory irregularity probably do not amount to more than 4 or 6 per cent. In general, it may be said, that the basal metabolism is lowered, that a decrease is from minus 10 to minus 26 per cent. Administration of antuitrin hypodermically caused little, if any, change, other than the slight rise from minus 10 to minus 7 per cent., either when given *directly* before the basal metabolism determination, or when administered steadily with orchic extract for weeks prior to the determination. In other words, neither a single dose nor the cumulative effects of many doses of antuitrin seemed to alter the basal metabolism.<sup>1</sup>

It seems not unlikely that the nasopharyngeal infection present during the second series of metabolism determinations produced a slight rise. Interpreted in the light of the polyglandular disturbance, the lowering of the basal metabolism indicates that the hypopituitarism present is of much greater intensity than the hyperthyroidism.

## PROGRESS NOTES

During the period of observation (six months) certain important additional facts were noted: (1) a marked susceptibility to infection; (2) the gradual development of a slight weakness of the shoulder group of muscles; (3) periods of somnolence; (4) a continuance of gain in weight until 250 pounds were attained in August, 1920; (5) an indolent reaction of the tissues in healing, with relation to the wound in the thigh, through which a specimen of muscle was obtained.

## TREATMENT

After a week of thyroid tablets, 0.065 gm., three times a day, dizziness, tachycardia (120), tremor and weakness appeared.

At another hospital, the patient was given whole gland hypophysis (Armour and Co.) over a period of three months. No improvement was noted. In fact, the patient thought he became worse, i. e., his weakness increased. No reduction of weight occurred during this time.

Various combinations of gland products were given in a variety of ways with no real improvement. Extract of whole pituitary gland (Armour and Co.) from 0.33 to 0.66 gm., three times a day, by mouth, with ampoules of antuitrin (Parke, Davis and Co.), 1 c.c., two, and then three, times a day, subcutaneously, together with orchic extract (Armour and Co.), 1 gm. a day

1. It is interesting to note that some very recent investigators<sup>2</sup> likewise noted no effect on basal metabolism from powdered anterior lobe hypophysis by mouth or extract of posterior lobe hypophysis and pars intermedia subcutaneously in a group of similar cases.

2. Snell, A. M.; Ford, F., and Rowntree, L. G.: Studies in Basal Metabolism, J. A. M. A. **75**:515 (Aug. 21) 1920.



by mouth, were given over a period of months without beneficial effect. Owing to the patient's sensitiveness to epinephrin and pituitary extract (posterior lobe hypophysis), the hypodermic administration of these drugs in doses as low as 0.18 c.c. each, three times a day, had to be discontinued.

The vomiting was well controlled by extract of belladonna, 1.2 c.c. five times a day, combined with bismuth subcarbonate, 0.66 gm. and sodium bicarbonate, 1.2 gm., four times a day.

Tincture of digitalis, in the usual dosages, was quite effective in relieving the edema of the legs.

#### DISCUSSION

1. *The Endocrine Balance.*—While there is no doubt that the picture presented is one of dystrophia adiposogenitalis, it is difficult to differentiate between the hypophysial and pure or primary genital forms of this disorder. Although there is very little evidence on which to involve the hypophysis, namely, no roentgen-ray changes in the sella turcia, no signs of intracranial pressure, no polyuria, no subnormal temperature, and no blood changes (such as eosinophilia,<sup>3</sup> lymphocytosis, low hemoglobin, as noted by Falta<sup>3</sup>), yet, the lowering of the basal metabolism possibly favors pituitary participation as against the pure gonadal or eunuchoid type.<sup>4</sup> The persistently open epiphyses of eunuchoidism are not found here, but as the onset of this affection occurred after epiphysial closure (i. e. after puberty), this differential point is of no avail.

It has been suggested<sup>5</sup> that two other gland disturbances may possibly produce this syndrome, namely, (1) an involvement of the suprarenal cortex; (2) the activity of ovarian rests.

Concerning the former, it may be said that a deficiency of the suprarenal cortex may well affect the genital status and the growth of the body and hair, but we have been unable to find sufficient evidence to postulate such involvement; the same is true of ovarian rests.

Of no little interest is the participation of the other ductless glands in this syndrome. Hyperthyroidism is evidenced by the increased tone of the vegetative nervous system, by the questionable enlargement of the gland, the epinephrin sensitiveness (the pronounced Goetsch test), the increased temperature and pulse rate, and, of most importance, the response to thyroid gland feeding (see Chart 1, Fig. 15). Of especial significance is the increased temperature, for uncomplicated hypopituitarism is accompanied by a *hypothermia*.

As for the gonadal participation, pronounced atrophy of the gonads is quite evident.

3. Falta, W.: *The Ductless Glandular Diseases*, Ed. 2, Philadelphia, P. Blakiston's Son & Co., 1916.

4. Falta states "many more investigations are necessary" in reference to this differential point.

5. Timme, W.: Personal communication.

For involvement of the pineal gland, we have the suggestive roentgen-ray shadow and the muscular dystrophy.<sup>6</sup>

Since we regard the white line of Sergent as being a very doubtful sign of hypoadrenia,<sup>7</sup> and with no other certain evidence of deficient suprarenal secretion, the participation of this gland seems very doubtful.

Claude and Gougerot<sup>8</sup> have considered a somewhat allied clinical syndrome some years ago under the caption of "Insuffisance pluriglandulaire endocrinienne," in which an instance of thyro-suprarenal-testicular deficiency was described.

Von Dziembowski<sup>9</sup> reports a case of dystrophia adiposogenitalis with muscular dystrophy in a young man of the same age with findings very similar to those here presented.

**2. Muscle Dystrophy.**—The relationship of the muscular dystrophies to endocrine disturbance was emphasized of late by W. Timme<sup>6</sup> and by Janney, Goodhart and Isaacson.<sup>10</sup> These authors have reviewed the literature on this subject. Timme emphasizes the rôle of the pineal gland; Janney and his co-workers note a polyglandular involvement in which the thyroid, hypophysis, gonads, pineal and supra-adrenals participate.

The latter workers have also drawn attention to the creatin—creatinin and sugar metabolism. In their series of dystrophy case, they found a marked decrease in the urinary preformed creatinin, the abnormal presence of creatin in the urine, low blood creatinin values with a normal amount of creatin in the blood, a hypoglycemia and a delay in the utilization of sugar.

In the case recorded above, there was a normal blood creatin, and the abnormal presence of creatin in the urine. The creatinin in the blood and urine is in normal amounts. This may be due to the limited extent of the dystrophy present in this case at the present time, with the preservation of a good deal of normal muscle function especially in the upper extremities. There is definite hypoglycemia,<sup>11</sup> and a delayed utilization curve present.<sup>12</sup>

In this connection the cardiac weakness manifested by this patient since the onset of the illness may be due to a cardiac involvement in

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6. Timme, W.: Progressive Muscular Atrophy as an Endocrine Disease, Arch. Int. Med. **19**:79 (Jan.) 1917.

7. Kay, W. E., and Brock, S.: The White Adrenal Line (Sergent): Its Clinical Significance, Am. J. M. Sc., to be published.

8. Claude, H., and Gougerot, H.: Insuffisance pluriglandulaire endocrinienne, J. de physiol. et path. gen., June, 1908.

9. Von Dziembowski, S.: Dystrophia Adiposo-genitalis mit Myopathie, Deutsch. med. Wchnschr. **43**:654, 1917.

10. Janney, N. W.; Goodhart, S. P., and Isaacson, V. I.: The Endocrine Origin of Muscular Dystrophy, Arch. Int. Med. **21**:188 (Feb.) 1918.

11. See blood sugar determination of March and May, 1920.

12. See blood sugar determination of August, 1920.

the dystrophic process, a point recently emphasized by Goodhart and Globus.<sup>13</sup>

3. *The Vegetative Nervous System.*—The reactions on the part of the vegetative nervous system indicate a marked hyperirritability, which is predominantly sympathicotonic as evidenced by the pronounced sensitiveness to epinephrin and to the other tests indicative of sympathetic dominance (Tables 1 and 2).

The significant disappearance of the white adrenal line (Sergent) following the administration of epinephrin, with its rapid reappearance deserves mention, the more so as the reappearance of the line occurred while the other manifestations of epinephrin action were still in marked evidence (tremor, cardiovascular symptoms and elevated blood pressure). This fact, as well as other investigations which are now being made on the white line, lead us to hesitate in accepting the alleged dependence of this phenomenon upon a state of hypo-adrenia.

4. *Complicating Infections.*—A noteworthy feature of the case is the patient's susceptibility and reaction to infection. While under observation he has had numerous nasopharyngeal and respiratory infections. In an attack of follicular tonsillitis the pulse rose to 160, respirations to 50, and the temperature to 105 F., remaining thus for forty-eight hours; periods of delirium accompanied the infection. *This indicates a distinct lack of immunity bodies.* The response to infection also reveals certain sympathicotonic characteristics in the symptomatology.

At this point the relationship of influenza to the production of this dysglandular disturbance may be considered. We believe that this individual had always been of the hypopituitary type, that the predisposition to a glandular dyscrasia was latent, and that the severe infection merely served to upset the balance to such a degree as to bring about the marked changes described.

*CASE 2.*—*A polyglandular syndrome on a definitely hereditary basis, in which a hyperfunctioning of the thymus and suprarenal glands counterbalances a hypopituitary state. Of especial interest are the physical manifestations, the increased muscular power, the roentgen-ray and laboratory findings. Attention is directed to the remarkable contrast offered between this case and Case 1.*

M. C., white, 20 years of age; prewar occupation, laborer. Habits: Negative for alcoholic excesses and drug addiction.

*Family History.*—Father, paternal grandmother and aunt are very stout, short in stature and possess a convergent strabismus similar to that shown by the patient. The father suffers from "asthma and rheumatism." Mother is small and thin; she has been operated on for gallbladder disease. Brothers:

13. Goodhart, S. P., and Globus, J. H.: On the Nature of Muscular Dystrophies, with a Report of Changes in Cardiac Muscle in Two Cases, *Neurol. Bull.* 1:386, 1918.

none. Sisters; one, living and well; she resembles the mother but not the father nor the patient.

*Personal History.*—He has had measles and influenza; the latter disease kept him in bed about two weeks. No gunshot wounds or other casualties. No venereal infection.

*Present History.*—The patient was sent to the hospital for mental observation, because of numerous escapades, and infractions of military regulations.

*Gastro-Intestinal:* Appetite voracious; does not care for candy or sweets. Vomiting, none. No gaseous or acid eructations. Bowels: Four or five movements a day.



Fig. 5 (Case 2).—Dystrophia adiposogenitalis.

*Respiratory:* No cough; no hemoptysis; no pain in the chest. Epistaxis, seldom.

*Nervous System:* Headache at times, located in forehead above the eyes; a dull pain getting better as the day progresses, inconstantly present, and sometimes absent for weeks. No especial nervousness; no dizziness; no fainting; no convulsive seizures.

Cardiovascular: Somewhat short winded, getting out of breath on running; no swelling of the feet; no palpitation of heart; no precordial pain.

Genito-Urinary System: Urinates about six times per day. No nocturia; no dysuria; no hematuria; no enuresis. Libido is apparently much diminished; states he entertains no feeling of sexual desire; nocturnal emissions absent. No history of coitus or homosexual practices.

*Physical Examination.*—The patient is of a short, stout build (Fig. 5), weighing about 180 pounds. The fat distribution is of an adiposogenitalis nature being noted especially in the breasts, lower abdomen, pubic regions and over the iliae. The skin over the abdomen and face is fine, smooth and silky. The breasts show a marked areolae formation.

Hair: The pubic hairs reveal a horizontal upper border simulating the female type. The hair is sparse over the abdomen, face and axillae; the hair on the face is limited to the chin and upper lip, being of the lanugo variety. The hair of the head and eyebrows is rather profuse; that over the lower back, buttock and thighs is considerable in amount, fine in texture and rather sharply delimited from the hairless parts above. Shaving is resorted to twice a week.

A definite degree of pigmentation is noted, especially about the waist and in the axillae.

The patient perspires very profusely.



Fig. 6 (Case 2).—The teeth.

Teeth: The teeth are definitely abnormal. In the upper row, the two central incisors are large; the left lateral incisor is erupted behind the left upper canine. The right upper canine is quite small and resembles an incisor. The lower incisors are irregularly erupted and stunted in growth. The first molars have a fang-like contour. Many cavities of small and large size and some pyorrhea alveolaris are present (Fig. 6).

Genitalia: Testicles are of medium size, situated near the external inguinal ring. The penis is normal in size and in power of erection.

Heart: The left border percusses out one inch beyond the nipple line; rate slow (80 per minute); rhythm regular. A soft systolic murmur is heard over the aortic area; it is not transmitted.

Blood Vessels: Negative.

Thyroid: Not enlarged.

Lungs: Slight dullness right base. No other abnormalities.

Abdomen: Negative.

Glandular and Osseous System: Negative.

*Neurologic Examination.*—1. Cranial Nerves: Eyes: Right affected with a convergent squint. Pupils: equal, round, regular in contour and reacting to direct and consensual light stimulation. There is some restriction of the field of vision of the right eye incident to the strabismus. No cranial nerve palsy.

2. Motor: *An unusual degree of muscle strength is exhibited by this individual.* He is able to lift and carry very heavy objects, seemingly out of

proportion to his height and general stature. (This capacity has influenced his choice of occupation. He has always worked at very laborious tasks as freight handling, etc.) No tremor is present.

3. Sensory: No abnormalities.

4. Reflexes: Normal; no abnormal reflexes.

5. Equilibration: Normal. No ataxia. No adiadokokinesis.

*Psychiatric Examination.*—This reveals a definite degree of mental deficiency, with the emotivity, suggestibility, and irresponsibility of a child.

#### ROENTGEN-RAY EXAMINATION

*Chest.*—Anteroposterior stereoroentgenogram (Fig. 7) shows a marked retraction in the right lateral aspect where there is a considerable thickening of the pleura; the costophrenic angles are clear. The upper mediastinum



Fig. 7 (Case 2).—Roentgenogram of the chest.

reveals a distinct thymus shadow. The right lung shows considerable clouding of apex. The bronchial trunks reveal considerable thickening. The left lung is negative. The apex does not give the impression of activity. The heart shadow appears moderately enlarged to the left.

*Hands.*—Anteroposterior view reveals the tapering form to the fingers and the small tufts characteristic of hypopituitarism (Fig. 8). The stereoroentgenogram of wrist joint, including carpus and metacarpus, shows that the epiphysis of the lower ends of the radius and ulna are not united firmly. There is an area of rarefaction at the proximal end of the second metacarpal bone on both sides. The femora and knee joints are negative.

*Head.*—The lateral stereoroentgenogram reveals a sella turcica which is quite shallow; anterior clinoid processes, which are shortened and blunted,

and a posterior wall seemingly eroded; the posterior clinoid processes are shortened and indistinct (Fig. 9).

*Gastro-Intestinal Tract.*—Fluoroscopic examination shows a slightly dilated stomach with lower border on level of crest of ilium. Stomach was hypotonic but began emptying in ten minutes. Emptied in midline. Examination of duodenum negative. The two and one-half and six hour plates each shows retention in the stomach. The six hour plate showed that the barium had passed entirely through the small intestines and was then present in the large bowel and rectum. The appendix was visualized in the twenty-four and forty-eight hour plates. The large intestines appear to be entirely empty in forty-eight hours.



Fig. 8 (Case 2).—Roentgenogram of the fingers of hypopituitarism.

The roentgen-ray findings in this case show that patient has a hypotonic stomach; hypertonic small intestines; a residual appendix. The large intestines empty in the normal time.

#### PHARMACOLOGIC TESTS (VEGETATIVE NERVOUS SYSTEM)

Pituitary Extract	Pulse	Blood Pressure	Symptoms
Before administration . . .	85	120-65	
Pituitrin, 1 c.c., hypo-			
dermically:			
15 min. later.....	84	125-85	Patient pale; no white line; slight red line
25 min. later.....	84	120-80	Patient pale; no other symptoms; slight red line. Temp. 98.8 F.
40 min. later.....	80	127-80	Patient still slightly pale; no other symptoms; slight red line.

## ATROPIN TEST

	Pulse	Blood Pressure		Symptoms and Signs
Before administration	80	Systolic 122	Diastolic 55	
Atropin sulphate, $\frac{1}{50}$ grain, hypodermically:				
10 min. later	80	120	70	Moderate dryness of mouth; pupils dilated; white line present, of moderate intensity.
20 min. later	90	115	65	Patient complains of dryness of mouth; no other symptoms; no flushing; extreme dryness; respiration, 35.
30 min. later	84	118	65	Mouth moderately dry; white line of moderate intensity; no especial symptoms or signs; oculocardiac reflex (Äschner's phenomenon) negative, i. e., no change in pulse; 90 to 86; pupils dilated.
1 hour later	80	122	60	Moderate dryness of mouth; slight dryness of skin; respiration, 26.
Before administration	85	135	60	
Atropin, $\frac{1}{100}$ grain:				
5 min. later	90	128	75	No symptoms.
7 min. later	90	130	70	No symptoms.
17 min. later	86	134	70	White line present, of moderate intensity on light pressure; red line on moderately deep pressure; no symptoms.
30 min. later	84	130	80	Slight dryness; white line present, of moderate intensity; red line of moderate intensity intermixed with white line on deeper pressure.
40 min. later	88	130	70	Slight dryness.

## PILOCARPIN TEST

	Pulse	Blood Pressure		Symptoms and Signs
Before administration	88	Systolic 138	Diastolic 40	White line present.
Pilocarpin, $\frac{1}{10}$ grain, hypodermically.				
10 min. later	88	138	40	Patient feels warm; salivation and perspiration moderate in degree.
25 min. later	88	138	40	Face flushed; moderate perspiration and salivation; marked red line not hitherto noted; white line present on light pressure, but diminished in intensity.
35 min. later	94	134	36	Slight salivation and perspiration; red line not nearly as marked; a mixture of red and white is obtained; white line of moderate intensity.



## EPINEPHRIN TEST

	Pulse	(Blood Systolic	Pressure— Diastolic	Symptoms and Signs
Before administration (10 min.)....	88	130	55	
Before administration (3 min.)....	86	132	60	
Epinephrin, 1 c.c., 1:1,000 solution, hypodermically.				
8 min. later.....	80	136	45	No especial symptoms.
20 min. later.....	82	138	45	Moderate palpitation of heart and throbbing of vessels; white line present; no especial subjective signs.
25 min. later.....	88	134	60	Quite marked palpitation and throbbing of vessels; no tremor; no subjective symptoms.
35 min. later.....	80	137	30	Palpitation and throbbing less marked; white line much diminished (hardly pres- ent); patient has "goose flesh" formation.
40 min. later.....	80	136	35	Still moderate throbbing of vessels; white line almost disappeared; red line pres- ent (no "goose flesh"); pa- tient makes no complaint of symptoms.

## MEASUREMENTS OF PATIENT

	Cm.
Total length .....	160.5
Circumference of head.....	53
Circumference of chest (at level of nipples).....	99
Circumference of abdomen (at umbilicus).....	99
Sternoclavicular junction to anterior superior spine.....	42
Anterior superior spine to internal malleolus.....	84
Anterior superior spine to upper border of patella.....	39.5
Acromion to styloid process of radius.....	49
Acromion to tip of olecranon.....	30.5
Distance between acromion processes.....	38
Distance between iliac spines.....	25
Span width.....	164.5
Penis (length).....	9.5
Testes, approximately .....	4 × 2.5
Thigh, left .....	54.5
Thigh, right .....	54.5
Calf, left .....	33
Calf, right .....	33
Arm, left .....	29
Arm, right .....	29.5
Torso-leg ratio .....	½ or .5

## LABORATORY DATA

	BLOOD	April, 1920	May, 1920
Erythrocytes .....		3,968,000	4,980,000
Hemoglobin, per cent.....		85	90
Leukocytes .....		10,200	9,700
Polymorphonuclears, per cent.....		72	72
Small mononuclears, per cent.....		22	16
Large mononuclears, per cent.....		4	12
Transitionals, per cent.....		2	..
Wassermann negative.			

## BLOOD SUGAR CURVE

	Blood Per cent.	Urine
Fasting .....	0.100	None
One hour after taking 132 gm. of glucose.....	0.108	None
Two hours after taking 132 gm. of glucose.....	0.121	Very faint trace

## CARBON DIOXID TENSION

65.5 volumes per cent.

## GASTRIC CONTENTS

Total acidity .....	70
Combined acids .....	6
Free hydrochloric acid.....	34
Combined hydrochloric acid.....	30
Lactic acid .....	Neg.

## FECES

Color .....	Brown
Consistency .....	Soft
Mucus .....	None
Occlt blood .....	Trace
Fat .....	Large amount
Starch .....	None
Muscle fibers .....	Few

## SUGAR TOLERANCE

Glucose, 200 and 250 gm., on fasting stomach, produces no glycosuria in the four hourly specimens taken following its administration.

## URINE

The urine is of an amber color; turbid; acid; specific gravity about 1.030; negative for albumin and sugar, and on microscopic examination.

## BASAL METABOLISM

Seventy-one and eight-tenths calories per hour; 40.3 calories per square meter per hour. Variation: plus 2 per cent. Essentially normal basal metabolism.

TABLE 2.—VAGOTONIA

	Case 1	Case 2	Case 3
1. Myosis.....	Negative	Negative	Moderate
2. Epiphora.....	Slight	Negative	Negative
3. Hyperhidrosis.....	Negative	Negative	Negative
4. Frequency of winking.....	Negative	Negative	Negative
5. Salivation.....	Negative	Negative	Negative
6. Gastric hyperacidity.....	Positive	Positive	Negative
7. Arrest of gastric secretion.....	Negative	Negative	Negative
8. Vomiting.....	Positive	Negative	Negative
9. Diarrhea (8 to 10 times).....	Negative	Positive	Negative
10. Gastric hypertonia.....	Positive	Negative	Negative
11. Spastic colon.....	Negative	Negative	Negative
12. Enopthalmos.....	Negative	Positive	Positive
13. Bradycardia.....	Negative	Negative	Positive
14. Low blood pressure.....	Negative	Negative	Positive
15. Asthmatic seizures.....	Negative	Negative	Negative
16. Esophagism.....	Negative	Negative	Negative
17. Mucous colitis.....	Negative	Negative	Negative
18. Dermatographia.....	Negative	Positive	Positive
19. Status thymicolymphaticus.....	Negative	Negative	Negative
20. Absent gag reflex.....	Negative	Positive	Positive
21. Eosinophilia.....	Negative	Negative	Negative
22. Pulsus irregularis respiratorius which disappears with atropin.....	Negative	Positive	Positive
23. Clammy hands and feet.....	Negative	Negative	Negative
24. Priapism.....	Negative	Negative	Negative
25. Oculocardiac reflex.....	Negative	Positive	Positive
26. Increased fat tolerance.....	Positive	Positive ?	Positive
27. Increased carbohydrate tolerance before and after epinephrin.....	Positive	Positive	Positive
28. Salivation induced by pilocarpin.....	Positive	Negative	Positive
29. Reaction to atropin.....	Positive	Negative	Negative

## DISCUSSION

1. *Endocrine Balance.*—*Suprarenal:* Hyperfunction of this gland is evidenced by the peculiar hairiness of the individual, slightly increased blood pressure, the increased muscular strength and possibly by the cardiac hypertrophy. The pigmentation noted might well be interpreted as having been deposited during a phase of hypoadrenia, either before the establishment of the present balance, or during upsets incident to infections.

*Thymus:* The definite thymus shadow indicates participation of this gland.

*Pituitary:* The peculiar adiposity, the shallow sella turcica, the increased sugar tolerance (evidenced especially in the alimentary tests) bespeak a definite hypopituitarism.

2. *Muscle Function.*—An increased muscle strength is noted, which, as has been mentioned, is out of proportion to his height and stature. In Case 1, which stands in peculiar contrast to this case, a muscular dystrophy was noted. While this case occurs in an individual in whom a distinct hereditary tendency may be traced, the first patient has no ascertainable hereditary basis.



Fig. 9 (Case 2).—Roentgenogram of the sella turcica.

It is difficult, if not impossible, in the present state of our knowledge, to explain satisfactorily the increased muscle strength of the one and the dystrophy of the other—to apportion to this or that gland even its relative importance, or to ascribe to any one gland, definite relationships to muscle function.

This uncertainty is enhanced not only by the multiplicity of glands playing a part, but also by the fact that complicated, subtle compensatory mechanisms are at work tending to establish a balance—attempting a restoration of normal function.



Fig. 10 (Case 3).—The relaxation difficulty in myotonia congenita. The facial expression is indicative of concentrated effort.

It is beside the purpose of this report to enter into the highly theoretical possibilities deduceable.

3. *Basal Metabolism*.—That a balance is struck in this disturbance of the endocrine system is again demonstrated by the essentially normal basal metabolism determination.

4. *Psyche*.—The mental deficiency and inadequate personality reactions present are dependent not on the endocrine dyscrasia but rather on a basic developmental and hereditary defect which involves the psyche on the one hand, and the glands of internal secretion and physical make-up (namely, congenital squint) on the other.

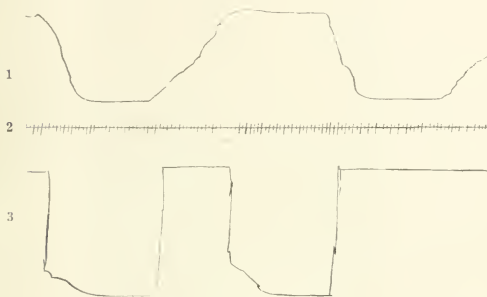


Fig. 11.—The normal and myotonic myogram. 1. The curve in myotonia congenita (Case 3). 2. The time markings in one-tenth second. 3. The normal curve. The downstroke represents contraction; the upstroke relaxation. The same amount of electrical stimulation was used in the myotonic as in the normal control.

*CASE 3.*—An instance of myotonia congenita associated with definite endocrine disturbances. A polyglandular syndrome involving a thyroparathyroid gonad deficiency on a probable hereditary basis is described.

R. L., aged 23 years, laborer. Habits: Tobacco and alcohol used in moderation. Drugs: None.

*Family History.*—Father living; suffering from cataract; mother living and well. Sisters: three, living and well. No history of epileptic seizures, psychiatric disorders, or any other diseases obtainable. No history of any muscular disorders.

*Previous History.*—Measles, scarlet fever and varicella in childhood. No venereal diseases.

*Present Illness.*—Ever since the age of 7 the patient has been subject to seizures, in which a tremor "comes on him." He then falls unconscious (?). He has never hurt himself in falling nor has he bitten his tongue, lip or cheek.

No involuntary passage of urine or feces has occurred. The seizures are of variable duration. On recovery he does not know his whereabouts and is confused. No feeling of fatigue or headache follow the seizures. They are infrequent in occurrence, sometimes being years apart.

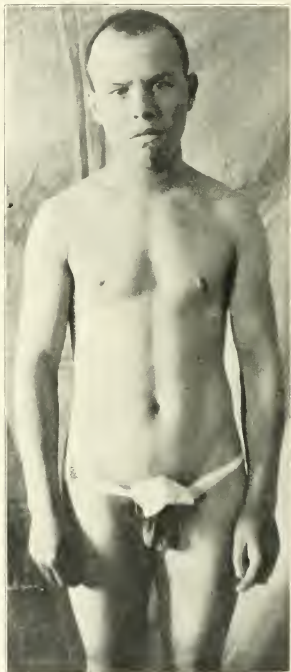


Fig. 12 (Case 3).—Dystrophia adiposogenitalis.

Ever since he can remember he has noted a peculiar difficulty in relaxing the grip muscles of his hands after grasping an object.

Gastro-Intestinal: Appetite good; no craving for sweets. Bowels: Two movements a day. No vomiting; slight gaseous eructations; no pyrosis.

Genito-Urinary: No dysuria or hematuria. No nocturia; no enuresis. Libido: definitely diminished as long as he can remember; he has never had sexual intercourse. No nocturnal emissions.

Respiratory: No cough, no epistaxis.

Cardiovascular: No shortness of breath, precordial pain, or distress. No easy fatigability; no edema of the legs.

Central Nervous System: No headache unless emotionally upset.

Skin: Shaves about two or three times a week although beard is ill-developed. Urticaria: None.

*Neurologic and General Physical Examination.*—No abnormalities in sensory, reflex or cranial nerve sphere.

*Motor:* A remarkable myotonia of the so-called myotonia congenita type (Thomsen's disease) is present; especially the grip muscles of the hand are involved making the relaxation of the grip a slow, difficult movement (Fig 10). This preponderating power of the flexors produces a position of the hand very similar to the accoucheur's hand of tetany, especially in the performance of fine movements (such as buttoning the shirt). The mechanical irritability of the muscles of the entire body is quite elevated, remarkable depressions being noted when muscles are mechanically stimulated; the muscle response on mechanical stimulation reveals a sustained plateau of contraction followed by a slow relaxation. This myotonic response is well marked in the tongue, and at times individual facial muscles may be made to undergo slow contraction.

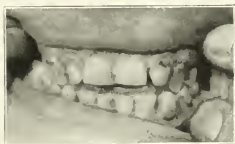


Fig. 13 (Case 3).—The teeth.

In the lower extremities the myotonia produces some slight stiffness in the performance of quick movements, such as rapid squatting movements. While fibrillary twitches are noted after mechanical stimulation, they are not nearly as marked as the myotonic depression. A greater degree of myotonia was noticed when the patient concentrated all his attention on his muscular efforts.

No Trousseau or true Chvostek phenomenon obtained.

*Electrical Examination.*—Faradic examination: As compared with controls, a stronger current was required to contract the muscles of the upper limbs. The reaction is definitely slower than normal, and is associated with a persistence of the contraction after removal of the current (myotonic reaction, Fig. 11).

Galvanic Examination: Normal quick response; KCC greater than ACC. Cerebellar Functions: Normal.

*Psychiatric Examination* reveals a definite mental deficiency, associated with a very labile emotional state. The suggestibility and lack of inhibition characteristic of the child are in marked evidence. Inability to remain in one place or concentrate on a given task is also characteristic. No other psychic abnormalities.

*General Physical Examination.*—The facies of the patient is that of a cretin, with a wide nasal bridge, thick lips, a mouth that is habitually open,

a large tongue which is slightly bifid. The eyes have a mongolian slant, and are somewhat deep-set with narrow apertures. A low forehead, quadrangular head and large mouth are noted (Fig. 12). The thyroid gland is definitely enlarged (isthmus and lateral lobes).

The hair of the head is dry and has a markedly convex curve at the forehead margin. The hair on the thighs and in the axillae is moderate in amount, but sparse on the trunk.

The skin and subcutaneous tissue are quite thick, as is very evident on attempts to draw blood or give a hypodermic injection. Dryness of the skin is also a feature.

While the penis is of normal size, the testes are distinctly undersized. The simulation of the labia minora by the scrotal folds is lacking. The pubic hairs are profuse and of a male type.



Fig. 14 (Case 3).—Roentgenogram of sella turcica

Examination of the teeth reveals upper central incisors which are very large in size; the lower incisors are normal. The lower and upper incisors do not approximate when the jaws are closed, the upper jaw protruding slightly. An elliptical area exists between the upper and lower incisors when the jaws are closed, in addition to the prognathism of the upper jaw. The canines are not fang-like and resemble the incisors. A marked pyorrhea alveolaris is present (Fig. 13). A high palatal arch is noted.

No hyperextensibility of the joints is present.

No adiposogenitalis type of fat distribution.

The terminal phalanges are definitely thickened, the nails are somewhat incurved.

Nose and Throat Examination: Except for a small spur on the left side of the septum, and a hypertrophied right inferior turbinate, the nose is normal.

The tonsils are slightly enlarged.



Hearing is normal in both ears. The labyrinthine reactions (Bárány) are normal although sluggish.

Eyes: Vision: right, 20/40; left, 20/40. Ocular movements good; right pupil larger, both pupils active to light and accommodation. Esophoria, 3 degrees. Right hyperphoria, 1 degree. Under homatropin: right, 20/70—100, axis 180 degrees; equals 20/50; left, 20/50—50, with plus 100, axis 90 degrees; equals 20/50. Both fundi negative. Perimetric examinations to form and color is normal. A compound myopia is present.

Lungs: Normal.

Heart: Normal.

Blood Pressure Observations: taken at 2 minute intervals:

Systolic	Diastolic
100	66
97	66
99	66
100	68
100	68

The pulse has been notably slow ranging in rate from 48 to 84, usually being in the sixties; a marked respiratory (sinus) arrhythmia is present. There is no edema or cyanosis.

Abdomen: No viscera palpable. Rectal examination reveals prostate flat, small, moderately firm.

Glands: No special adenopathy noted.

Temperature Observations: A definite subnormal temperature, ranging between 97 F. in the morning and 98 F. in the afternoon has been observed daily for weeks.

#### MEASUREMENTS OF PATIENT

	Cm.
Total length .....	165
Circumference of head.....	55
Circumference of chest (at level of nipples).....	87.5
Circumference of abdomen (at umbilicus).....	77
Sterno-clavicular junction to anterior superior spine.....	39
Anterior superior spine to internal malleolus.....	82
Anterior superior spine to upper border of patella.....	41.5
Acromion to styloid process of radius.....	51.5
Acromion to tip of olecranon.....	29.5
Distance between acromion processes.....	36
Distance between iliac spines.....	24.5
Span width .....	168
Penis .....	12
Testes .....	2 × 1.5
Thigh, right .....	49.5
Thigh, left .....	49.5
Calf, right .....	33
Calf, left .....	33.5
Arm, right .....	27.5
Arm, left .....	27.5
Torso-leg ratio .....	39/82 or .47

#### LABORATORY DATA

##### BLOOD

	Feb. 11, 1920	May, 1920
Erythrocytes .....	4,200,000	4,320,000
Leukocytes .....	6,700	8,500
Hemoglobin, per cent.....	90	80
Differential count:		
Small mononuclears, per cent.....	22	16
Large mononuclears, per cent.....	8	13
Polymorphonuclears, per cent.....	70	71

## BLOOD CHEMISTRY

Blood sugar (fasting stomach), 0.106 per cent. (106 mg. per 100 c.c. of blood).  
 Blood sugar (116.9 gm. of glucose given), 0.136 per cent. (136 gm. per 100 c.c. of blood).  
 Blood urea: 40 mg. per 100 c.c. of blood.  
 Blood creatinin: 1.875 mg. per 100 c.c. of blood.  
 Blood calcium: 10.6 mg. per 100 c.c. of blood (Dr. K. M. Vogel).  
 Blood carbon dioxide: 62.4 volume per cent.  
 Blood Wassermann reaction negative Jan. 8, 1920, and Feb. 12, 1920.  
 Bleeding time: 2 minutes.  
 Coagulation time: 6 minutes.

## FECES

March 1, 1920: Color, brown; consistence, medium; mucus, negative; blood, negative; muscle fiber, striated and nonstriated present; fat, present; starch, negative.

March 3, 1920: After the ingestion of 200 gm. fat in the form of butter: Color, brown; consistence, medium; mucous, negative; blood, negative; muscle fiber, none found; fat, present. No appreciable increase over that found on previous examination. Starch, negative.

## STOMACH CONTENTS

	Feb. 28, 1920	March 1, 1920
Total acidity .....	18	34
Combined acidity .....	3	4
Free hydrochloric acid.....	0	12
Combined hydrochloric acid.....	10	18
Lactic acid .....	Faint trace	Negative
Blood (gross and occult).....	Negative	Negative

## SPINAL FLUID

Pressure, normal; transparency, slight admixture of blood (technic); cell count, normal, discounting presence of blood; globulin, no material increase; Wassermann, negative. Colloidal gold test, normal curve for preliminary and final curves.

## URINE

Numerous urine examinations made at varying intervals revealed: Amber; clear; acid, with a specific gravity varying between 1.026 and 1.036; albumin, sugar, acetone and casts were not found in any of the examinations. No polyuria. Phenolsulphonethalpin showed 45 per cent. output for first hour, 25 per cent. output for second hour, a total of 70 per cent.

## SUGAR TOLERANCE TEST (ALIMENTARY GLYCOSURIA)

No glycosuria after 100 gm. glucose, after 180 gm. and after 200 gm. glucose (given in 430 c.c. of milk equaling 30 gm. of lactose).

No glycosuria in the first hour, after 230 gm. glucose (with 1 c.c. of 1:1,000 solution epinephrin given one-half hour later). Glycosuria very positive two hours later; glycosuria less positive three hours after that; glycosuria still less positive four hours later.

After three weeks of thyroid gland feeding (from 6 to 9 grains a day), 100 gm. glucose were given in the morning with no thyroid gland tablets; no glycosuria resulted. On the following morning, 3 grains thyroid gland was given by mouth, followed by 100 gm. glucose in one-half hour; a very faint trace of sugar was noted in the urine collected, following the above procedure.

## BASAL METABOLISM

Calories per square meter per hour, 39.9. Variation plus 1 per cent.

## ROENTGEN-RAY EXAMINATION

No abnormalities noted in bones and joints; all epiphyses are firmly united.

Fluoroscopic examination shows a rather large stomach with its lower border one inch below the intercristal line. It is slightly hypotonic with no filling defect apparent. The duodenal cap appears to have a filling defect which is inconstant. The ileum is pulled over slightly to the right of the median line. There is no six hours retention. The twenty-four hour plate reveals the barium still in the cecum. The forty-eight hour plate reveals an almost empty intestine. Roentgen findings suggest a large slightly hypotonic stomach with probably periduodenal adhesions; in addition there appears to be some pericecal adhesions.

The chest reveals a slight broadening of the mediastinal shadow (thymus?).

Examination of the skull reveals a small sella turcica with a posterior clinoid process which is definitely thickened. A suggestive pineal shadow is found (Fig. 14).

Hands: The tuft of the left thumb is considerably smaller than that of the right; the other tufts are equal in size, but slightly smaller than usually seen.

## ATROPIN TEST

	Pulse	Blood Pressure— Systolic Diastolic	Respira- tion	Symptoms and signs
Before administration ....	44	105 60	20	Pulse shows marked respira- tory arrhythmia.
Administration of $\frac{1}{16}$ s grain				
20 min. later.....	44	90 60	20	No dryness of mucous mem- brane; respiratory arryth- mia less marked.
30 min. later.....	48	95 65	20	Slight dryness of tongue; respiratory arrhythmia al- most entirely disappeared.
45 min. later.....	54	95 70	20	Moderate dryness of tongue
1 hour later.....	56	102 65	20	Same.

## ERGOTIN TEST

	Pulse	Blood Pressure— Systolic Diastolic	Signs and Symptoms
Before administration .....	64	100 70	
Ergotin, $\frac{1}{10}$ grain.....	..	..	No reaction was noted fol- lowing this drug.

## ESERIN TEST

	Pulse	Blood Pressure— Systolic Diastolic
Before administration .....	72	105 70
Eserin, $\frac{1}{50}$ grain		

Following the administration of this drug, no gastro-intestinal effects were noted, the only reaction was slight headache.

## PILOCARPIN TEST

	Pulse	Blood Pressure— Systolic Diastolic	Respira- tion	Symptoms and Signs
Before administration ....	58	100 60	22	
Administration of 0.008 gm.				
10 min. after.....	70	90 55	22	Feels warm; face consider- ably flushed; slight perspi- ration.
18 min. after.....	60	100 60	22	Face moderately flushed; considerable perspiration; moderate salivation; a feel- ing of warmth noted; re- spiratory arrhythmia un- changed.
24 min. after.....	62	100 60	22	Feels cooler; moderate per- spiration; slight salivation; desire to urinate present.
30 min. after.....	62	100 60	22	Feels cool; no salivation; perspiration much less, slight on forehead; face less flushed; temperature, 97.4 F.

## PILOCARPIN TEST (REPEATED)

	Pulse	Systolic (Blood Pressure)	Diastolic	Signs and Symptoms
Before administration .....	60	100	65	
Pilocarpin, $\frac{1}{40}$ grain				
10 min. after.....	60	96	60	Moderate flushing of face; slight salivation and moisture of skin; complaints of headache.
15 min. later....	60	100	60	Skin moderately moist, moderate salivation.
25 min. later...	60	100	60	Face moderately flushed, skin moist, salivation fairly marked.
30 min. later...				Skin moist, salivation fairly marked; patient exhibited psychic changes after administration of drug; began to cry and stated he was worried over his mother; said he was "hurting with sorrow."

## EPINEPHRIN TEST

	Pulse	Systolic (Blood Pressure)	Diastolic	Respiration	Signs and Symptoms
Before administration ....	58	102	70	16	Considerable respiratory arrhythmia.
1 c.c. of 1:1,000 solution hypodermically					
10 min. later.....	52	102	70	15	No tremor no general reaction.

## PITUITARY TEST

	Pulse	Systolic (Blood Pressure)	Diastolic	Signs and Symptoms
Before administration .....	64	100	70	
Pituitrin, 1 c.c.				
5 min. later.....	64	100	70	
10 min. later....	64	100	70	Patient pale; desires to urinate.
20 min. later...	64	100	70	Desire for defecation present; movement of bowels occurred.

Thermo-reaction (Cushing) negative, i. e., no rise in temperature after injection of pituitrin (1 c.c.).

## TYRAMIN

	Pulse	Systolic (Blood Pressure)	Diastolic	Signs and Symptoms
Before administration .....	54	100	60	
Tyramin, 60 mg.				
5 min. later.....	40	110	64	
12 min. later....	44	105	60	Blood pressure rise very slight

Narrow slits; enophthalmos; tendency toward myosis; gag reflex lessened. Oculocardiac phenomenon positive pulse, 64, slowed to 48. Winking infrequent. Epinephrin into conjunctival sac, negative. Goetsch's test (intracutaneous injection of epinephrin) negative.

## DISCUSSION

1. *The Endocrine Balance.*—The cretin facies, the enlargement of the thyroid gland, the subnormal temperature, the increased sugar tolerance, the thick skin, the hypotonic vegetative nervous system, and the insensitiveness to large amounts of thyroid gland feeding, are conclusive evidences of a hypothyroidism.

The testicular atrophy reveals the gonadal deficiency.

The parathyroid involvement is suggested by the mytonia (see below) in this connection the occurrence of double cataract in the father at the age of 48 might be construed as a parathyroid defect.

The rôle of the thymus is uncertain.

2. *Mytonia Congenita.*—The association of this remarkable motor disorder with endocrine disturbances has been noted before. W. Falta writes of this relationship under diseases of the parathyroid gland and

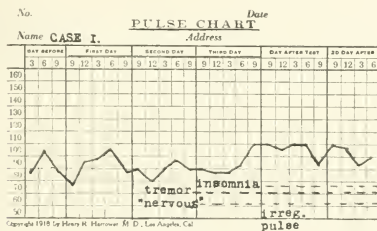


Fig. 15.—The response to ascending doses of thyroid gland (Harrower's test).

notes the presence of mytonia in certain cases of tetany; he states that "just those animals in whom thyroid and parathyroids have been removed show these manifestations," i. e. mytonia. Steinert,<sup>14</sup> speaking of the closely allied mytonia atrophica, emphasizes the atrophy of the testicles and impotence in his cases.

It will be noted that the mytonia in this instance is associated with a very definite thyrogonadal deficiency.

14. Steinert: Ueber das klinische und anatomische Bild des Muskelschwunds des Myotoniker, Deutsch. Ztschr. f. Nervenhe. **37**:58, 1909.

Certain American authors have likewise called attention to the dependence of this myopathy on endocrine disturbances.<sup>15</sup>

3. *Metabolism*.—The essentially normal basal metabolism again demonstrates the fact that the hypothyroidism is compensated for by the activity of the other glands and possibly through the agency of other mechanisms less understood.

As for the calcium metabolism, we have not had the facilities at hand to estimate this, with the detail with which Rosenbloom and Cohoe<sup>16</sup> have accomplished it. These authors concluded from their studies that a "loss of calcium may play a part in the production of the symptoms of myotonia congenita."

The increased sugar tolerance is noted in the alimentary tests. Of interest is the reduction of sugar tolerance with the consequent appearance of a slight glycosuria after the oral administration of three grains of thyroid gland (see laboratory data); this seems to show in a conclusive way the dependence of increased sugar-tolerance upon thyroid deficiency in this case.

4. *The Psyche*.—The mental deficiency and inadequate personality reactions present in this case point again to a basic hereditary developmental defect which affects both the psyche and ductless glands.

#### THERAPEUSIS

For over a period of one month he was given first 6 grains and then 9 grains of thyroid gland a day, together with  $\frac{1}{10}$  grain parathyroid gland, three times a day, and potassium iodid, 5 minims, three times a day. Under such therapy there was no appreciable change in the myotonia. Hoffmann (quoted by Falta), in a case of myotonia associated with tetany, noted the disappearance of the myotonia on the administration of thyroid gland and its reappearance after withdrawal, while the tetanic symptoms were not affected.

There was an increased psychomotor activity—purely a quantitative increase, however; the same psychic abnormalities (childish behavior, emotional instability and irresponsibility) were still in evidence. He stated that he had some difficulty in getting asleep, and that he felt warm at night. No tremor, tachycardia, loss of weight or diarrhea occurred, nor were there any changes noted in the configuration of the thyroid gland. A coryza due to the iodid necessitated a discontinuance of this drug for a time.

15. McCouch, G. P., and Ludlum, S. D. W.: Is Myopathy Related to Disorders of Internal Secretion? *Med. Rec.* **39**:1042, 1916.

16. Rosenbloom, J., and Cohoe, B. A.: Clinical and Metabolism Studies in a Case of Myotonia Congenita-Thomsen's Disease. *Arch. Int. Med.* **14**:263 (Aug.) 1914.

## CONCLUSIONS

1. Three unusual cases are presented in detail, in each of which remarkable endocrinopathies are associated with unusual manifestations in the muscular system.

2. Attention is directed to the endocrine balance, the sugar and the basal metabolism.

3. It is shown that the basal metabolism is the result of the sum total activities (in part compensatory), of the various ductless glands. In polyglandular disorders, such as those described, the basal metabolism does not reflect the degree of participation of any individual gland.

4. In two cases a congenital developmental defect is postulated as the cause of both the endocrine deficiencies and the psychic disorders.

To Drs. George Draper and Henry E. Marks we owe our especial thanks for most of the laboratory findings, and for valuable advise.

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## BLOOD VOLUME IN PERNICIOUS ANEMIA \*

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Blood volume in pernicious anemia has been studied but little, and the results obtained have been at considerable variance. Of the literature concerning blood volume, only that portion bearing on pernicious anemia is considered in this paper. Various methods have been followed, such as the dye method of Keith, Rowntree and Geraghty,<sup>1</sup> the carbon monoxid method of Haldane and Smith<sup>2</sup> and those methods such as Quincke's<sup>3</sup> and Lindeman's,<sup>4</sup> based on the consideration of the red cells before and after transfusion. The dye method of Keith, Rowntree and Geraghty is based on the concentration in the blood of a dye injected intravenously which remains in the circulation for a long time. From this the plasma volume can be calculated and by the hematocrit readings the total blood volume determined. In three determinations made in cases of pernicious anemia they found the total volume in two to be decreased and in the third a normal total volume with a markedly increased plasma volume.

The carbon monoxid method consists in the inhalation by the subject of a known volume of this gas and the determination of its percentage saturation in the blood. From this the total capacity of the blood for carbon monoxid can be found and this is synonymous with total oxygen capacity. It can possibly be best explained by an example. A patient having absorbed 100 c.c. of carbon monoxid, it is found that his blood is 20 per cent. saturated by this gas. The total capacity, then, for carbon monoxid is 500 c.c. and as the oxygen capacity is the same as that of carbon monoxid, that is likewise 500 c.c. The oxygen capacity of the patient determined previous to the administration of carbon monoxid is 20 per cent. The total blood volume is calculated as follows:

$$\frac{500}{20} \times \frac{100}{100} = 2,500$$

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\* From the Medical Clinic of the Peter Bent Brigham Hospital, and the Harvard Medical School. This is Study No. 12 of a series of studies on the Physiology and Pathology of the Blood from the Harvard Medical School and allied hospitals.

1. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: *Arch. Int. Med.* **16**: 547 (Oct.) 1915.

2. Haldane, J., and Smith, J. L.: *J. Physiol.* **25**:331, 1899.

3. Quincke, H.: *Deutsch. Arch. f. klin. Med.* **20**:27, 1877.

4. Lindeman, E.: *J. A. M. A.* **70**:1209 (April 27) 1918; *ibid.*, 1292.



This method was used in the study of pernicious anemia by Lorraine Smith,<sup>5</sup> who found that the total amount of hemoglobin was reduced in proportion to the severity of the disease and that the plasma might either be increased or diminished. He concluded that those patients with increased total volume were worse symptomatically than those with a more concentrated blood.

Quincke's and Lindeman's methods depend on the changes produced by transfusion in the number of red cells. Quincke calculated blood volume from the red count of the donor's blood and the amount given. The red count is not sufficiently accurate to give good results.

Lindeman centrifuged equal specimens of the donor's blood and that of the patient before and after transfusion of large amounts of blood. The principle is the same as that of Quincke but the results are more accurate. He found the blood volume in pernicious anemia to be always reduced but more in some cases than in others, and concluded that when the total volume is only slightly reduced the symptoms are fewer though the relative anemia be severe. This conclusion as to the relation of symptoms to volume is in absolute variance with that of Lorraine Smith.

It is obvious that if we had any one element in the blood which we could determine with absolute accuracy, the blood volume could be measured by the change in concentration of that element produced by transfusion. This would be true provided vaso-motor changes produced by the transfusion were not of any great extent. In the present study, I have used the oxygen capacity of the blood, as it most nearly represents the ideal of an element which can be measured accurately. The method is simply the determination of the oxygen capacity of the patient's blood immediately before and three minutes after the completion of the transfusion. The oxygen capacity of the citrated blood of the donor is determined and from these three factors and the volume of blood given, the total blood volume is calculated as follows:

A = oxygen capacity of patient's blood before transfusion.

B = oxygen capacity of patient's blood after transfusion.

D = oxygen capacity of the citrated blood administered.

Q = quantity given in cubic centimeters.

$$V = \frac{D-B}{B-A} \times Q$$

Oxygen determinations were made with the Van Slyke blood gas pump.<sup>6</sup> The blood sample taken before transfusion was obtained from

5. Smith, J. L.: *Tr. Physiol. Soc. London* **51**:311, 1900.

6. Van Slyke, D. D.: *J. Biol. Chem.* **33**:127, 1918.

the needle through which the blood was subsequently given. That taken after was obtained from the opposite arm two or three minutes after the last of the blood had been introduced. About 500 c.c. of blood was usually given.

In order to test the accuracy of this method a few experiments were done on blood in vitro. The oxygen capacity of sheep's blood was determined, salt solution added (about 10 per cent. of the total amount of blood), and the oxygen capacity redetermined.

#### PROTOCOLS OF EXPERIMENT

EXPERIMENT 1.—Sheep's blood, 226 c.c., to which (Q) 22 c.c. of normal salt solution was added; (A) oxygen capacity before addition = 24.66; (B) oxygen capacity after addition = 22.36. The formula for a simple dilution

$$\text{such as this is } \frac{V}{V+Q} = \frac{B}{A}$$

$$\frac{V}{V+22} = \frac{22.36}{24.66}$$

$$24.66 V = 22.36 V + 491.92$$

$$2.30 V = 491.92$$

$$V = 214 \text{ c.c.}$$

Error about 5 per cent.

EXPERIMENT 2.—457 c.c. sheep's blood. (A) Oxygen capacity = 18.97 per cent. Forty-five c.c. salt solution added. (B) Oxygen capacity = 17.15 per cent.

$$\frac{V}{V+45} = \frac{17.15}{18.97}$$

$$18.97 V = 17.15 V + 771.75$$

$$1.82 V = 771.75$$

$$V = 424 \text{ c.c.}$$

Error, 7 per cent. minus.

EXPERIMENT 3.—450 c.c. sheep's blood. (A) Oxygen capacity = 19.26 per cent. Forty-five c.c. physiologic sodium chlorid solution added. (B) Oxygen capacity = 17.46 per cent.

$$\frac{V}{V+45} = \frac{17.46}{19.26}$$

$$V = 437 \text{ c.c.}$$

Error, 3 per cent. minus.

Blood from a patient suffering from congenital heart disease with polycythemia was used in a further set of experiments in vitro. In this case the blood was diluted to represent an anemia and transfusion done in the test tube with the usual oxygen determinations made on the various samples.

EXPERIMENT 4.—(A) 490 c.c. of diluted blood with an oxygen capacity of 10.59 per cent.

(D) To the above 45 c.c. of blood with an oxygen capacity of 32.62 per cent. was added.

(B) Oxygen capacity of the mixture = 12.37 per cent.

$$V = \frac{32.62}{12.37} - \frac{12.37}{10.59} = 45$$

$$V = 512$$

Correct  $V = 490$ .

Error, 4 per cent. plus.

(A) 500 c.c. diluted blood with an oxygen capacity of 4.85 per cent.

(D) To this 50 c.c. of blood with an oxygen capacity of 19.19 per cent. was added.

(B) Oxygen capacity of this mixture is 6.01 per cent.

$V = 568$  c.c. Should be 500 c.c., an error of 13 per cent. plus. This error was thought to be due to insufficient addition of normal blood, so the experiment was continued.

(A) To 452 c.c. of diluted blood with an oxygen capacity of 6.01 per cent.

(D) 70 c.c. of blood added having an oxygen capacity of 19.19 per cent.

(B) Oxygen capacity of the mixture is 7.86 per cent.

$$V = \frac{19.19}{7.86} - \frac{7.86}{6.01} \times 70 = 430 \text{ c.c.}$$

It should be 452 c.c., making an error of about 5 per cent. minus.

From these test tube experiments with dilution and concentration of blood it is seen that the changes produced in oxygen capacity are sufficient to give a fairly accurate determination of volume. To a dilute blood at least 10 per cent. of a normal blood must be added in order to produce changes in the oxygen capacity which are sufficient to permit calculation of the volume.

The total blood volume of ten patients who were transfused for pernicious anemia was determined by the method described. Also, for comparison, their total blood volume was calculated on the basis of the body weight which, according to Keith and Rowntree's figures for the normal, is 85 c.c. of whole blood per kilo body weight. This is referred to as the theoretical volume.

#### REPORT OF CASES

CASE 1 (Med. No. 11710).—H. H. McK., aged 42, clerk, married. Diagnosis: pernicious anemia.

Patient entered hospital Sept. 18, 1919, complaining of weakness. During the last three years patient has had periods of weakness lasting from one to two months, some of which prevented him working. Three months ago he had a much more severe attack, during which he lost all appetite and was forced to stop work. Numbness of hands present for last six or seven weeks. Gradually getting pale. Weight three months ago, 62 kg.

Physical examination shows little but lemon yellow pallor, irregular pupils which react, a smooth glistening tongue, and a palpable liver. Gastric analysis shows anacidity. Blood smear typical of primary anemia. No nucleated forms.

Transfused September 24 with 500 c.c. citrated blood having an oxygen capacity of 18.89 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	6.13%	33%	980,000
After transfusion.....	7.92%	42%	1,440,000
Total blood volume = 3,064 c.c.			
Theoretical volume = 4,541 c.c.			

Transfused October 7 with 510 c.c. of citrated blood having an oxygen capacity of 20.89 per cent. Some blood spilled so figures are not accurate. This illustrates the fact that small errors may make a large difference in the result.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	9.65%	52%	1,480,000
After transfusion.....	11.85%	64%	2,300,000
Total blood volume = 2,095 c.c. Weight unchanged.			

Transfused October 14 with 560 c.c. of citrated blood having an oxygen capacity of 21.66 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	13.24%	71.6%	2,424,000
After transfusion.....	14.57%	78.8%	2,660,000
Total blood volume = 2,985 c.c.			

Patient left the hospital considerably improved and could do a fair amount of walking without palpitation or dyspnea. Reentered December 14 with practically all the complaints of his first admission. No edema noted.

Transfused December 18 with 475 c.c. of citrated blood having an oxygen capacity of 20.46 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	4.90%	26%	1,300,000
After transfusion.....	7.08%	38%	1,600,000
Total blood volume = 2,915 c.c.			

Transfused January 6 with 510 c.c. of citrated blood having an oxygen capacity of 20.43 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	7.60%	40%	1,766,000
After transfusion.....	9.20%	49%	2,244,000
Total blood volume = 3,548 c.c.			

Assuming that the volume calculated was correct, the proportion of donor's blood to the patient's can easily be figured. In the determination of December 18, it is 1:6.13, and in that of January 6 it is 1:6.96. If, then, the blood of the donor and that of the recipient are mixed in the test tube in these proportions, an oxygen capacity identical with that found after transfusion should result provided the volume is correct. This was done and the following results were obtained:

	Dec. 18	Jan. 6
Oxygen capacity after transfusion.....	7.08%	9.20%
Oxygen capacity of the test tube mixture..	7.08%	9.20%

Furthermore, January 6 the theoretical volume on the basis of 85 c.c. per kilo body weight was calculated and found to be 4,590 c.c. If this were the true volume, the proportion of donor's blood to that

of the recipient would be 1:9. Such a mixture was made and a reading of 8.52 per cent. oxygen capacity obtained, thus showing that the volume must be considerably less than the calculated normal of Keith and Rowntree.

CASE 2 (Med. No. 11799).—G. K., aged 53, clerk; entered hospital Nov. 24, 1919, complaining of weakness. Lived in China for thirty years and contracted sprue five years ago since when he has had severe diarrhea controlled more or less by santonin. Weight five years ago, 214 pounds; present weight, 135 pounds. Has lost 10 pounds in the last three months. Seven months ago had three intravenous arsphenamin injections for sprue, following which he became very weak, jaundiced and anemic. Diarrhea continued. Physical examination negative, except for yellowish pallor, small fresh hemorrhage in fundus of left eye. Tongue pale; smooth. Abdomen slightly distended, but liver and spleen not palpable. No edema. No free hydrochloric acid in gastric contents. Severe and persistent diarrhea, with from three to ten stools per day.

Transfused October 3 with 460 c.c. of citrated blood having an oxygen capacity of 20.92 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	10.19%	54%	1,620,000
After transfusion.....	11.08%	59%	Not done
Total blood volume=	5,086 c.c.		
Theoretical volume=	4,879 c.c.		

Transfused October 17 with 550 c.c. of citrated blood having an oxygen capacity of 22.55 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	10.12%	54%	1,520,000
After transfusion.....	11.45%	61%	2,160,000
Total blood volume=	4,588 c.c.		

Transfused October 24 with 612 c.c. of citrated blood having an oxygen capacity of 23.18 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	12.11%	65%	2,220,000
After transfusion.....	13.92%	75%	2,540,000
Total blood volume=	3,131 c.c.		

During the period between October 17 and October 24, there was an intense diarrhea which might account for some lowering of blood volume; however, this last volume being so much lower, was checked in the test tube by adding donor's blood to recipient's blood in the proportion calculated from the volume, namely, 1:5.11. This gave a reading of 14.32 per cent. instead of 13.92 per cent. oxygen capacity, thus showing that the volume is too low. A mixture was then made in the proportion of 1 c.c. of donor's blood to 8.8 c.c. of the recipient's before transfusion, which proportion is based on a volume calculated on the basis of body weight, 5,440 c.c. This gives a reading of 13.03 per cent. oxygen capacity which is considerably under the figure 13.92 per cent. obtained after transfusion.

CASE 3 (Med. No. 12013).—T. M., aged 49, male; entered the hospital Oct. 11, 1919, complaining of weakness and anemia. One sister has a similar anemia. Onset of present illness was in April, 1919, with palpitation and dyspnea and dizziness. Physical examination negative, except for pallor and characteristic tongue.

Transfused October 14 with 620 c.c. of citrated blood having an oxygen capacity of 23.02 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	5.99%	32%	840,000
After transfusion.....	7.81%	42%	1,360,000
Total blood volume = 5,096 c.c. Weight of patient = 82 kg.			
Theoretical volume = 6,960 c.c.			

Transfused October 29 with 534 c.c. of citrated blood having an oxygen capacity of 22.61 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	5.36%	29%	Not done
After transfusion.....	7.17%	38%	Not done
Total blood volume = 4,552 c.c.			

Patient left the hospital unimproved and died November 18.

CASE 4 (Med. No. 12235).—M. A. P., aged 55, housewife; entered the hospital Nov. 10, 1919, complaining of weakness, palpitation, swelling of the feet, hands and abdomen. She has had two similar attacks which were less severe, the first, three and one-half years ago, and the second about ten months later, both of which were less severe than the present attack. Last illness began nine months ago and for the last few months there has been a gradual increase in edema. Physical examination shows typical pallor and tongue and a general anasarca.

Transfused November 14 with 358 c.c. of citrated blood having an oxygen capacity of 19.92 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	10.31%	55%	1,370,000
After transfusion.....	11.70%	62%	1,640,000
Total blood volume = 2,117 c.c.			

Theoretical volume = 3,485 c.c. (Calculated on body weight after loss of edema.)

A mixture of the donor's blood and that of the patient before transfusion in the proportion found from the volume gives a reading of 11.34 per cent. oxygen capacity in place of 11.70 per cent. This indicates that the volume calculated is too low.

Transfused November 25 with 508 c.c. of citrated blood having an oxygen capacity of 18.71 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	6.68%	36%	1,750,000
After transfusion.....	8.49%	45%	1,950,000
Total blood volume = 2,870 c.c.			

A mixture of donor's and patient's blood in the proportion obtained from this volume gives a reading of 8.49 per cent. oxygen capacity. It is of interest that during the time between the two transfusions the patient lost about 4 kg. of her edema which loss continued until it was all gone. The total loss was 17 kg. At the time of the second transfusion she was clinically improved although her blood shows a distinct falling off in hemoglobin percentage. The increase in volume may be due to a fluid entering the blood with a consequent dilution.

CASE 5 (Med. No. 11111).—J. A., aged 58. Diagnosis: pernicious anemia. Entered hospital with symptoms of weakness, dizziness and dyspnea dating back three months. At this time he showed a typical picture of pernicious anemia. He had a spontaneous remission and was well up to April, 1910, when the old symptoms began to recur. Weakness and pallor are now his principal complaints.

Transfused June 3 with 710 c.c. of citrated blood having an oxygen capacity of 18.05 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	6.36%	34%	808,000
After transfusion.....	8.74%	47%	1,464,000
Total volume = 2,780 c.c. Weight of patient = 51.6 kg.			
Theoretical volume = 4,386 c.c.			

CASE 6 (Med. No. 11822).—R. F., aged 58, housewife. Diagnosis: pernicious anemia. Entered hospital Sept. 11, 1919, complaining of weakness, ringing in the ears and dyspnea. Two years ago she noticed weakness and pallor and loss of weight. This has increased gradually and for the last four months she has had palpitation and dyspnea. Physical examination shows typical pallor, smooth tongue, an enlarged heart and a systolic murmur. The spleen is palpable. No free hydrochloric acid in stomach contents.

Transfused September 26 with 510 c.c. of citrated blood having an oxygen capacity of 19.23 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	7.64%	41%	1,500,000
After transfusion.....	9.03%	48%	2,200,000
Total blood volume = 3,742 c.c. Weight of patient, 58.2 kg.			
Theoretical volume = 4,947 c.c.			

Discharged greatly improved.

CASE 7 (Med. No. 12208).—C. A. L., aged 56, housewife. Diagnosis: pernicious anemia. Entered hospital Sept. 11, 1919, complaining of weakness and anemia. Onset was seven years ago with weakness as the principal symptom. She has had several remissions during this time and for the last few months has noticed pallor, abdominal distress, dyspnea and marked weakness. Physical examination showed yellow pallor, heart slightly enlarged, liver and spleen palpable, tongue smooth. Gastro-intestinal roentgenograms negative. Free hydrochloric acid absent in stomach contents. Blood picture typical of pernicious anemia.

Transfused November 10 with 491 c.c. of citrated blood having an oxygen capacity of 21.02 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	5.81%	31%	2,780,000
After transfusion.....	7.65%	41%	2,830,000
Total blood volume = 3,568 c.c. Patient's weight, 50 kg.			
Theoretical volume = 4,250 c.c.			

A mixture of donor's blood and that of the patient made in a test tube in the proportion of 1:7.26 which is the relation of the two provided the volume calculated is correct. This mixture has an oxygen capacity of 7.88 per cent. in place of 7.65 per cent., the amount found after transfusion. This would indicate that the true volume is slightly higher than the one calculated.

Patient discharged unimproved.

CASE 8 (Med. No. 12313).—A. S. P., aged 61, clerk. Diagnosis: pernicious anemia. Entered hospital Nov. 20, 1919, complaining of weakness, anemia and swelling of legs. Two and one-half years ago had an attack of anemia and weakness lasting six weeks, and another similar attack one year ago lasting two months. He was well and at work between attacks and up to June, 1919, when symptoms reappeared in a more severe form with edema and dyspnea. At entrance, he shows a marked edema of the extremities with fluid in both pleural cavities and abdomen, a yellow pallor of the skin and smooth glossy tongue.

Transfused December 3 with 600 c.c. of citrated blood having an oxygen capacity of 21.74 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	4.43%	24%	908,000
After transfusion.....	6.74%	36%	.....
Total blood volume = 3,900 c.c. Patient's weight, 68 kg.			
Theoretical volume = 5,780 c.c.			

CASE 9 (Med. No. 2322).—M. C., aged 50, housewife; entered hospital Nov. 21, 1919, complaining of weakness. Onset about one year ago with weakness, dyspnea and palpitation. Has run down steadily, but except for loss of appetite and weight there have been no further symptoms. Physical examination shows typical pallor, a smooth but not glossy tongue and a palpable spleen. There is anacidity of the gastric contents and a blood picture typical of primary anemia. Weight three years ago, 195 pounds; present weight, 134 pounds.

Transfused November 25 with 528 c.c. of citrated blood having an oxygen capacity of 17 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	8.88%	48%	1,880,000
After transfusion.....	10.01%	54%	2,030,000
Total blood volume = 5,280 c.c. Patient's weight, 61 kg.			
Theoretical volume = 5,185 c.c.			

CASE 10 (Med. No. 10324).—M. C., aged 50; entered the hospital Dec. 19, 1919, complaining of dyspnea and anemia. Onset of symptoms about January, 1918. These consisted of weakness, pallor and dyspnea on exertion. Has been transfused several times and had two definite periods of improvement during the first of which his blood reached normal. For two months before his present admission all the symptoms have been worse and edema of the legs and epigastric distress are marked. Physical examination shows typical pallor, tongue and blood picture. There is anacidity of the gastric contents, also ascites and edema of the legs.

Transfused January 10 with 521 c.c. of citrated blood having an oxygen capacity of 21.15 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	7.99%	43%	1,048,000
After transfusion.....	9.35%	50%	1,272,000
Total blood volume = 5,742 c.c.			

Transfused January 15 with 495 c.c. of citrated blood having an oxygen capacity of 19.94 per cent.

	Oxygen Capacity	Hb.	Red Cell Count
Before transfusion.....	7.03%	37%	1,275,000
After transfusion.....	8.16%	44%	1,808,000
Total blood volume = 5,160 c.c. Patient's weight, 59 kg.			
Theoretical volume = 5,015 c.c.			

#### RELATION OF PLASMA AND CELLS

Hematocrit determinations were done in most of the cases and in the following table the results are given expressed in cubic centimeters per kilo body weight.

It is quite evident that the reduction in total volume is due to the decrease of red cells rather than to any change in plasma volume. Cases 9 and 10 show a normal total volume and in one of these in which the hematocrit determinations were made, the normal volume



is shown to be due to an increase of plasma. This is in conformity with the findings of Keith, Rowntree and Geraghty. The average plasma volume is, however, normal. Case 9 shows a high volume per kilo and Case 4 the lowest. The degree of anemia in the two cases was essentially the same. Case 4 had a general anasarca which was diminishing rapidly and Case 2 a very severe and persistent diarrhea.

## RESULTS OF HEMATOCRIT DETERMINATIONS IN TEN CASES

Case	C.c. Blood Per Kg. Body Weight	C.c. Plasma Per Kg. Body Weight	C.c. Cells Per Kg. Body Weight
1	56	45	11
2	72	59.5	12.5
3	62	56	6
4	52	46.5	5.5
5	54	Not done	Not done
6	64	Not done	Not done
7	71	60.5	10.5
8	57	50	7
9	88	75.5	12.5
10	86	Not done	Not done
Average .....	66	56	10
Average normal .....	85	50	35

## SUMMARY AND CONCLUSIONS

1. A method for calculation of blood volume is described.
2. By this method nineteen determinations were made in ten cases of pernicious anemia.
3. The total blood volume in these cases was reduced in all but two cases.
4. Plasma volume remains essentially normal, the decrease in total volume being due to loss of cell mass.
5. The case showing a normal total volume has a high plasma volume.
6. There is no noticeable relation between the severity of the disease and the decrease in total volume.

## A SIMPLE DEVICE FOR MEASURING RATE OF METABOLISM \*

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Of those laboratory tests useful in the diagnosis of certain forms of disease, perhaps none is more valuable to the clinician than the recent test devised to measure basal metabolism.

The sudden interest which the test has stimulated among clinicians has spread with surprising rapidity, perhaps for the reason that, from the standpoint of efficiency in the differentiation of certain disease, its results are so spectacular in uniformity and conclusiveness. Moreover, it was just this rapid spread of interest in the test which has so effectually confirmed its usefulness as a diagnostic aid. The question as to its value, so far, has been singularly free from controversy.

Lusk <sup>1</sup> and his associates, on the basis of very accurate and elaborate measurements, have emphasized chiefly the scientific aspects of the test.

The problem of making the test available to those clinicians not having access to the elaborate equipment of the nutrition laboratory was solved by Benedict,<sup>2</sup> who designed a portable apparatus for measuring the basal metabolism of human subjects, and by DuBois,<sup>3</sup> who has devised a "linear formula" for use in indirect respiration calorimetry.

In a recent article, McCaskey <sup>4</sup> says of the method originated by Benedict: "Unless its clinical value can be shown to be commensurate with the time, labor and equipment required, and in this instance these items are rather large, it cannot and should not endure." His paper is offered as an additional contribution to this end. In other words, he believes that the urgent need for such a test justifies the fairly considerable expenditure of time, labor and equipment necessary to its performance.

To extend still further its usefulness by reducing to a minimum this expenditure of time, labor and equipment, I undertook to devise an apparatus which is simple and accurate in operation and yet sufficiently compact for the surgeon, clinician or general practitioner to carry it to the patient's home or bedside, an apparatus which is portable in a practical sense. In designing it, I have kept this feature constantly in mind.

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\* From the Department of Pathology and Bacteriology, University of Illinois College of Medicine.

1. Lusk: Arch. Int. Med. **15**:793 (May) 1915.

2. Benedict: Boston M. & S. J. **178**:667, 1918.

3. DuBois: Arch. Int. Med. **15**:793 (May) 1915; **17**:855 (June) 1916.

4. McCaskey: J. A. M. A. **74**:927 (April) 1920.

A second feature also deserves special emphasis in this connection. All mathematical computations have been eliminated. The units expressing the results of the test are arrived at immediately and without calculation. A method which involves the use of logarithms, slide rule and considerable time for calculations, as in the case of the Benedict method, has not properly considered the inability of the average busy clinician to deal with this kind of mathematical procedure.

#### PRINCIPLE OF THE METHOD

The ratio of the quantity of carbon dioxide eliminated to the quantity of oxygen consumed is called the respiratory quotient. In the oxidation of fat this R Q (respiratory quotient) is about 70:100, or 0.70; of carbohydrate it is 100:100, or 1. Obviously, when a combination of fat and carbohydrate is oxidized, the R Q lies somewhere between 0.70 and 1. It is necessary to know the R Q because the

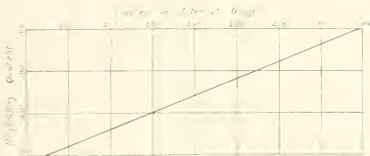


Figure 1.

caloric value of a liter of oxygen, a factor which must be known, varies with the R Q, as shown in Figure 1.

With appropriate apparatus, the determination of the R Q, i. e., the amount of carbon dioxide eliminated and oxygen consumed, is an ordinary laboratory procedure. Having determined the R Q, reference to Figure 1 gives the caloric value of each liter of oxygen so consumed. The number of liters of oxygen consumed,<sup>5</sup> multiplied by the caloric value of one liter at this R Q then gives the total caloric radiation or rate of metabolism.

In figure 1 it is seen that the caloric value of oxygen is not markedly affected by varying the value R Q. In fact, in clinical work, it is

5. A measure of the carbon dioxide eliminated could also be made the basis for calculating the heat output according to this same reasoning. The objections to this method, however, are that the caloric value represented by the elimination of a liter of carbon dioxide varies too widely, depending on whether it was derived from the burning of fat or of carbohydrate, and also to the fact that irregularities in the respiration causing overventilation of the lungs increase this error in determinations extending over such short periods.

customary to assume the  $RQ$  as 0.82, which has been found to be the average of a large number of determinations. By so doing, the task of measuring the carbon dioxide to ascertain the ratio is obviated, and it is necessary then only to measure the oxygen intake.

To calculate the caloric output by measuring the rate of oxygen intake and multiplying this by the caloric value of one liter at the assumed  $RQ$  of 0.82 is, therefore, the principle on which the apparatus here described is designed to operate.

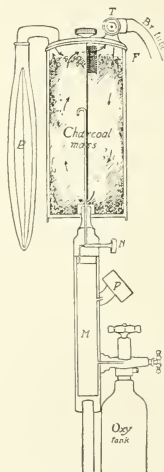


Fig. 2.—Cross-section of apparatus: Arrows indicate direction of movement of inspired and expired air; Br. tube, breathing tube; T, three-way cock; F, flutter valve for directing circulation of gases; b, rubber bag to contain measured amount of gas and to allow for expansions and contractions in respiration; N, needle valve for releasing the measured amount of oxygen from M, the measuring cylinder, into the charcoal-alkali tower above; P, pressure gauge with room temperature scale on dial to indicate when one liter of dry oxygen at 0 C. and 760 mm. has been released at any given room temperature from the oxygen tank.

#### CLINICAL APPLICATION OF THE METHOD

There are three principal ways in which the living body expends its store of heat. 1. Following the ingestion of food there is a marked

rise in the rate of heat loss due to the specific dynamic action of foods. 2. Muscular exertion requires an expenditure of its caloric equivalent. Its effect on the heat loss ceases with complete muscular relaxation usually within thirty minutes following ordinary muscular effort. 3. Certain vital processes, such as respiration, circulation, secretion, the maintenance of body temperature, etc., must be supported irrespective of the first two and at the expense of the food stores or tissues of the body.

The first two represent variable quantities and may be eliminated by fasting and muscular relaxation, as indicated above. However, the third is a remarkably constant quantity for a given individual. Ordinarily this regular and ever present demand for the maintenance of the vital functions amounts to more than one-half of the body's daily expenditure of heat; and because of the constancy with which it takes this toll, even in conditions of extreme starvation it has been given the name basal metabolism.

Under conditions of basal metabolism, the rate of heat loss of different individuals is surprisingly similar. It varies with sex and age, being higher in youth and in males, but these factors need only to be taken into account to determine what is normal in any given case. So true is this, that when the basal metabolism of a given individual varies more than 10 per cent. from the normal for that patient's sex and age, certain diseases may be diagnosed on the basis of this change from the normal rate.

#### DESCRIPTION OF THE APPARATUS

The apparatus (Fig. 2) consists merely of a mouthpiece with wide flexible tube leading the expired air into the apparatus; a tower of small pieces of charcoal, soaked in alkali, for the purpose of removing the carbon dioxide; a gas anesthetic rubber bag to allow for expiration and inspiration and to contain the oxygen supply; a piece of aluminum pipe serving as a support to the alkali tower, and also as a measuring apparatus for delivering into the rubber bag a known quantity of oxygen. The measuring cylinder is also provided with an attachment for the small forty gallon oxygen cylinder, and with a pressure gage with special dial to indicate when the desired quantity of oxygen has been released.

The instructions which have been found to cover the points in technic and principle of the method sufficiently to enable one of ordinary skill to carry out the test are as follows:

#### PREPARATION OF THE PATIENT

(1) Have subject take no food (nothing but water), for from fourteen to eighteen hours previous to test, preferably from 6 o'clock evening meal, to 10 o'clock next morning, when test is made.

(2) Subject should be lying comfortably and quietly from fifteen to thirty minutes before test begins.

#### TECHNIC OF THE TEST

Attach nose clip and test for air leak at nose by having subject close mouth and exert moderate pressure. Turn three-way cock open to air. Insert rubber shield of mouth piece inside of lips but outside of teeth, drawing lips up about neck of mouth piece. Open needle valve of measuring cylinder. Admit gas slowly from oxygen tank until bag distends sufficiently to just touch the side of the alkali tower. This quantity is used merely to establish what is called the *beginning point*. Now close needle valve. Admit gas *slowly* again



Fig. 3.—Apparatus in use.

from oxygen tank while indicator is driven around, and, after tapping gage with finger, stands exactly over room temperature point of scale on dial. When released, later, this quantity will be 1,000 c.c. ( $\pm 2$  c.c.) of gas at 0 C. and 760 mm. Hg. It is held in the measuring cylinder ready for release at the *beginning point*. Approximately at *beginning of expiration* quickly turn three-way cock closed. Subject is now breathing gases confined in the tower and bag. Observe the quantity of gas in bag as it gradually diminishes in volume. Watch point where bag makes contact with the side of alkali tower. That expiration, when the bag, at its fullest distention, just fails to touch the side of alkali tower, is counted *one*. If the expiration following this one fails to cause the bag to touch the alkali tower it is counted *two*; and the one following this *three*. This establishes the *beginning point*. At this instant release

the stop watch and then discharge the 1,000 c.c. of gas now in measuring cylinder by opening needle valve. Close needle valve again and admit a second liter of gas into measuring cylinder. After a few minutes bag will have again diminished in volume to same condition described for the beginning point (namely, three successive normal expirations, when the bag, at its fullest distention, just fails to touch side of alkali tower). Watch for this as before and when it occurs note time by stop watch. Release second liter to bag, as before. Close needle valve again and admit a third liter to measuring cylinder. Proceed in this way, observing exact time required by subject to consume each successive liter. Two liters is usually sufficient but average of three is better. Finally at the end point of the last liter used, stop the watch, turn three-way cock to open, and remove the mouth piece. Before removing nose clip, test again for air leaks as at beginning of test. (If air leak has developed during test discard the readings.) Total time on watch divided by number of liters consumed equals *average time required to consume one liter*, and from this the subject's rate of metabolism is made known as follows:

#### TO CALCULATE METABOLIC RATE

To illustrate: Male, age, 30; height, 66 inches; nude weight, 153 pounds; averaged 3.1 minutes to consume 1 liter of oxygen. Referring to Table 1, his height and weight lines intersect in a point between oblique lines 1.7 and 1.8, say at 1.79; 1.79 square meters is, therefore, his body-area. Referring to Table 2, this body-area line, 1.79, and his 3.1 minute line, intersect in a point between 50 and 55, say 53. Rate is, therefore, 53 calories per square meter per hour or + 34 per cent., i. e., 34 per cent. above the normal for his age and sex, as seen from Table 3.

#### CARE OF ALKALI TOWER

Pour about 400 c.c. of a *saturated* solution of commercial sodium hydrate over coal mass. About 100 c.c. of this will settle to bottom. A few minutes before beginning on a test, hold back coal particles with hand and drain this bottom fluid into a glass or beaker, then pour it over coal mass again to redistribute the alkali. Run the test and duplicate test, then drain this bottom liquid off again and discard it. For another test and duplicate test use another fresh 100 c.c. portion of the alkali solution. After test, drain and discard as before. Before putting apparatus away always drain off this bottom fluid, and then pour in about 200 c.c. water to wash off the exhausted alkali on the coal particles. Drain this off, and then pour in another 200 c.c. water to stand in bottom of tower until used again. This prevents crystallization of sodium bicarbonate in bottom and clogging of coal mass. Before using apparatus again, drain this water off and pour on about 100 c.c. of saturated solution of sodium hydrate, which will be sufficient for a test, and duplicate test, as before.

The height-weight table (Fig. 4) is modified after the table of DuBois<sup>3</sup> according to his "linear formula":  $\text{Area} = W^{0.425} \times H^{0.725} \times 71.84$ .

The body area-minute table (Fig. 2) is constructed according to the formula  $\frac{4.823 \times \text{liters of oxygen consumed per hour}}{\text{Surface area of patient}} = \text{calories per hour per square meter}$ , in which 4.823 is the caloric value of one liter oxygen at the assumed  $RQ$  0.82, and in which the liters of oxygen consumed per hour was calculated on the basis of the average number of minutes required by the patient to consume one liter of oxygen.

## SOURCES OF VARIATIONS

1. *Age and Sex.*—The effect of age and sex on the rate of metabolism is shown in Table 1 by Aub and DuBois.<sup>6</sup>

TABLE 1.—VARIATIONS DUE TO AGE AND SEX, EXPRESSED AS CALORIES PER SQUARE METER PER HOUR

Age	Males	Females
14-16.....	46.0	43.0
16-18.....	43.0	40.0
18-20.....	41.0	38.0
20-30.....	39.5	37.5
30-40.....	39.5	36.5
40-50.....	38.5	36.0
50-60.....	37.5	35.0
60-70.....	36.5	34.0
70-80.....	35.5	33.0

In expressing the rate of metabolism as  $\pm\%$ , the above factors must therefore be taken into account.

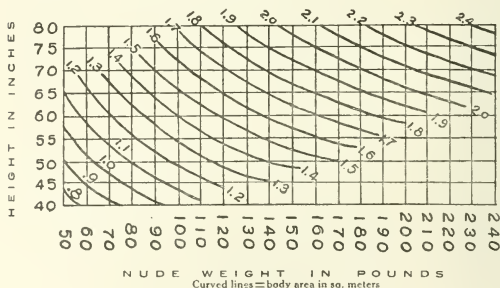


Fig. 4.—Height-weight table.

2. *The Effect of Foods.*—The specific dynamic action of food may be defined as that effect which the ingestion of food has in stimulating the metabolic rate to an increase above the basal rate. For proteins this stimulating action amounts to an increase of 33 per cent. of the caloric value of the amount of protein ingested; for fats it is 11 per cent, for carbohydrates, 5 per cent. The patient is instructed to take no food after the six o'clock evening meal, the test being made at about 10 o'clock the next morning, i. e., sixteen hours after the last meal. If these instructions are not made clear, or the subject forgets, or uses deception in regard to them, this specific dynamic action of food enters as a source of considerable variation, and may take the observer unawares. Another source of error which may also

6. Aub and DuBois: Arch. Int. Med. 19:831 (July) 1917.



take the observer by surprise is that due to the effect of caffeine<sup>7</sup> in increasing the rate of metabolism. If the patient is allowed his morning cup of coffee or tea on the assumption that it contains nothing of any food value, the observer is then at a loss to explain the 10 or 20 per cent. rise above the normal basal rate.

3. *Muscular Tension and Psychic States.*—The effect of muscular tension in increasing the rate of metabolism is obvious. If the subject is restless, or lies in an uncomfortable or tense position, or is subjected to various psychic disturbances as fear of the test, or embarrassment, the effect in increasing the metabolism above the basal rate may be even greater than in the last mentioned source of variation. For example, in a demonstration of this apparatus given before the Chicago Society of Internal Medicine, the subject's rate rose to 28 per cent. above her basal rate; which later, under less exciting conditions, was normal. In spite of her attempts to assume complete muscular relaxation, the rate of metabolism, more than anything else, revealed the attack of stage fright, which the subject later admitted. Some day the criminologist, by the aid of appropriate controls and setting, may find in this stimulating action of fear a dependable ally in the detection of crime. The point of therapeutic value is that a patient, put to bed to reduce his rate of metabolism, defeats the purpose in a large measure, sometimes by worry, by homesickness, by entertaining visitors, or by a number of other ways in which the psychic element has not been considered.

4. *Variations Due to Certain Diseases.*—When the basal rate of metabolism of a subject is found to be constantly above or below the average basal rate for persons of his age and sex, certain diseases are diagnosed, chief among which are disturbed functions of the thyroid and pituitary. Severity of the disturbance is proportional to the variation from the normal rate, and, therefore, by following the variation of the rate from the normal by successive tests, the effect of therapy can be demonstrated. Following the effect of treatment is, in fact, one of the firmly established uses of the test.

#### TECHNICAL SOURCES OF VARIATIONS

THE GAS MEASURING APPARATUS: The purpose of the pressure gage is to indicate that pressure at which the measuring cylinder will deliver 1,000 c.c. of dry oxygen at 0 C. and 760 mm. Hg pressure. This volume at 23 C. and 750 mm. Hg becomes 1,098.8 c.c.; if measured over water it is further increased to about 1,128.8 c.c. since the vapor tension at 23 C. is 21 mm. Hg. In operation, however, this

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7. Means, Aub and DuBois: Arch. Int. Med. **19**:832 (July) 1917.

measuring apparatus is independent of temperature and pressure changes. The influence of temperature on the gas volume is eliminated by having the pointer of the gage come to rest over various points on the dial representing various room temperatures. The construction of the measuring apparatus is essential in principle to that of the anaeroid barometer, and is, therefore, independent of changes in atmospheric pressure, i. e., the indicator merely represents the tension of gas inside the cylinder as against the tension outside of it, regardless of what this outside tension may be. In spite of these features, the apparatus is not a delicate mechanism requiring frequent readjustment

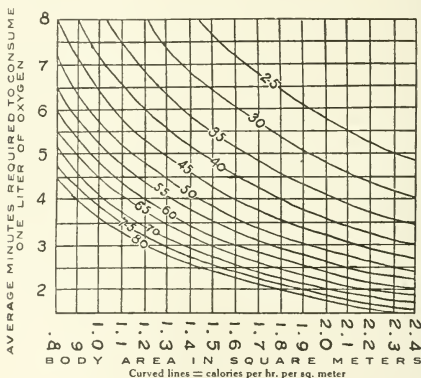


Fig. 5.—Body area-minute table.

or repair. By actual trial the accuracy of the measurement is about  $\pm 2$  c.c. out of 1,000 c.c., or 0.2 per cent. error. This degree of accuracy is possible, however, only if the operator is careful each time when reading the pressure to tap on the side of the gage with the tip of the finger, to make sure that the indicator has not encountered some slight resistance in its cog mechanism.

(b) EFFECT OF OXYGEN RICH AIR ON RATE OF OXYGEN ABSORPTION: Benedict and Higgins<sup>8</sup> have shown that the breathing of oxygen rich air, even up to 90 per cent. oxygen, has no effect on the rate of oxygen absorption. The concentration of oxygen in the

8. Benedict and Higgins: *Am. J. Physiol.* 28:1, 1911.

test as described here is never above about 80 per cent. at the beginning, and never below 20 per cent. at the end of the test.

(c) EFFECT OF TEMPERATURE: The effect of temperature on the volume of gas contained in the alkali tower is very slight. The rise in temperature averages only 2 C. and the volume of the contained air is only about from 500 to 700 c.c. Error from this source is negligible.

(d) THE NOSE CLAMP: Special caution is necessary in adjusting the nose clamp. If too tight, the patient is in considerable distress in a few moments; if too loose enormous errors will result, since the air of expiration is forced out through small leaks very rapidly. The patient should use only moderate pressure, however, in testing for such leaks. To guard against this source of error, consistent care in adjusting the nose clamp is absolutely essential, regardless of the type of nose clamp employed.

TABLE 2.—VARIATIONS IN END-POINTS IN SUCCESSIVE TESTS ON THE SAME INDIVIDUAL, WITHOUT DISCONNECTING THE SUBJECT FROM THE APPARATUS\*

Test	Stop-watch	Minutes	Percentage Variation from Average
1	4.71	4.71	0.4
2	9.34	4.63	1.5
3	14.01	4.67	-0.4
4	18.76	4.75	-1.3
5	23.42	4.66	-0.4
6	28.04	4.62	-1.5
7	32.72	4.68	-0.2
8	37.46	4.74	+1.1
9	42.15	4.69	0.0
10	46.90	4.72	+1.5

\*The patient from whom these data were obtained was in coma, showing that knowledge on the test or cooperation on the part of the patient is not essential to accuracy.

(e) THE END POINT OF THE TEST: The volume of gas in the bag is reduced at the rate of about 15 c.c. per respiration. The bag, therefore, approaches the empty condition gradually. Moreover, the point in the cycle of respiration which gives us the beginning and end-point, namely, the end of expiration, is also constant regardless of the rate and amplitude of respiration, since this point in the cycle represents the position of passivity of the respiratory organs.

The percentage variation in the time required by the patient to consume each successive liter is usually within  $\pm 2$  per cent. of the average of the total time, as seen in Table 2. In patients suffering from severe degrees of thyreotoxicosis who are invariably more or less intractable and restless, it is, therefore, of greater importance, clinically, to make two separate duplicate one liter tests, than a single test of two or more liters in succession. In this way the method is rendered practically free from chance errors due to the operator's technical routine.

## COMPUTING THE TOTAL CALORIC REQUIREMENTS OF THE PATIENT

When the total caloric loss of an individual under basal metabolism conditions is determined (Fig. 6) for the twenty-four hour period, this does not mean that this caloric equivalent in food will keep him in caloric equilibrium, even with complete rest in bed. A subject with a caloric output of 1,600 calories for twenty-four hours will require about 400 calories in addition to offset the caloric waste caused by the specific dynamic action of the food. This additional amount of food will depend on the proportion of the various food elements since these vary, as stated before, in their effect in stimulating the

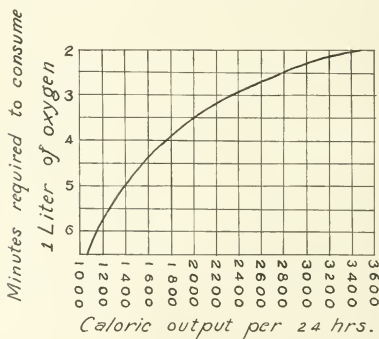


Figure 6.

metabolism above its basal rate. Ordinarily, their combined effect amounts to a waste of between from 20 to 25 per cent. of the total caloric intake. If the subject is not at rest in bed, a still further addition in the caloric intake must, of course, be allowed, the amount depending on the amount of work done by the subject. This is of importance in connection with the regulation of the diet of patients who are abnormally low or high in body weight.

## COMPARATIVE TESTS

In comparing the results of tests made by this apparatus with those obtained by the Benedict apparatus, the two instruments agree within very narrow limits. Strict agreement in the reading of the gas volumes could not be expected since the oxygen volume as measured by

the Benedict method is made over water and no allowance made for aqueous tension. This, at 23 C., introduces an error of 3 per cent. in the reading by the Benedict apparatus, and at higher temperatures the error would be disproportionately greater. When correction is made for this factor, the liter of gas, as measured in the apparatus described here, when discharged into the spirometer in the Benedict apparatus showed a rise of the spirometer corresponding very closely to one liter as measured in the latter. With successive tests the agreement was extremely close,  $\pm 3$  or 4 c.c. when the same end of the spirometer was used. Three different models of the Benedict apparatus were used in this comparative test with equally close results.

TABLE 3.—BASAL RATE IN CALORIES PER SQUARE METER PER HOUR \*

Subject	Age	Sex	Rate
S. T. ....	25	F	36.5
W. ....	26	F	37.0
J. J. T. ....	32	M	39.6
L. P. G. ....	24	M	39.6
F. G. ....	22	F	37.5
M. W. ....	16	F	41.0
S. P. ....	13	M	44.0

\* These results should be compared with the values given in the table by Aub and DuBois (Charts 1 and 2).

TABLE 4.—PERCENTAGE RISE ABOVE BASAL RATE \*

Patient	Age	Sex	Rise, per Cent.
C. C. H. ....	35	M	+112
H. P. ....	47	F	+ 87
P. P. ....	28	F	+ 51
F. C. ....	28	M	+ 35
W. S. ....	52	F	+ 63
A. H. ....	44	F	+ 26
M. P. ....	38	F	+ 22

\* The rates given in this table are those of persons suffering from hyperthyroidism of varying degrees of severity. All of them had been diagnosed as such by Dr. Charles S. Williamson before being tested. The results show the same ranges of variation reported by others on many cases of this disease.

TABLE 5.—PERCENTAGE RATES OF METABOLISM WITH BENEDICT AND JONES APPARATUS

	Benedict	Jones
Miss G. H. ....	104-107	103-101
Miss S. F. ....	157-160	158-150
Mr. N. A. ....	99-102	98-99
Miss E. P. ....	123-120	120-121
Mr. H. L. ....	103-105	104-107

In comparing the percentage rates of metabolism of normal persons, and also hyperthyroid subjects showing varying grades of severity, the values shown in Table 5 represent the usual degree of agreement of the two instruments, when the particular instrument in use is protected against leaks, and when the carbon dioxid absorbing reagent is working properly.

The conclusion is, therefore, justified that either apparatus is quite satisfactory for clinical studies in metabolism, the question of differences in the two instruments centering mainly around the proposition of arriving more easily and quickly at the end result with less chance for error when operated by persons of only average skill.

This instrument has also been used for many months in hundreds of tests on normal persons of all ages and both sexes. The results agree (within the limits of physiological variation) with the average values of normal subjects of given age and sex (see table by Aub and DuBois given on a preceding page). As reported in a previous paper,<sup>9</sup> the apparatus is also being used regularly by the author in clinical research and also in the diagnosis of suspected or borderline cases of myxedema and hyperthyroidism. Duplicates of the instrument have been distributed among clinicians and general practitioners in various parts of the country, who are using it for a like purpose. So far no inherent inaccuracies or technical difficulties have been reported from these sources.

#### SUMMARY

An apparatus for measuring the rate of oxygen consumption, designed to be portable in a practical sense, is described and illustrated.

Sources of error are discussed and their percentages reduced to a minimum consistent with simplicity.

Mathematical procedures necessary for calculation of the rate of metabolism (from the respiratory quotient, the body area, and the rate of oxygen consumption) are eliminated from the test. The reading is made directly, in terms of calories per hour per square meter of body area.

Independent and comparative tests show its technical variations to be within physiologic and individual variations, and, therefore, adequate to the needs of the clinician as an instrument for measuring basal metabolism.

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9. Jones, H. M.: *J. A. M. A.* **75**:538 (Aug. 21) 1920.

## SPIROCHETAL PULMONARY GANGRENE \*

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Ever since Obermeier, in 1873, reported the presence of micro-organisms of the genus spirocheta, or spirilla, in the blood of patients with relapsing fever, many diseases have been found to be caused by varieties of this species. The most important disease due to spirochetal infection is, of course, syphilis, to which etiologic relationship of the *Spirochaeta pallida* was demonstrated by Schaudinn and Hoffman in 1905. Castellani subsequently found that frambesia tropica, or yaws, was caused by the *Spirochaeta pertenuis*. The etiologic relationship of spirochetes to Vincent's angina, Weil's disease, rat bite fever and pyorrhea alveolaris has likewise been demonstrated.

It is, however, not so well known that certain pathologic processes in the bronchi and lungs are due to the activity of these micro-organisms. Many years ago, Eichhorst stated that he found spirochetes in the sputum of some patients suffering from bronchitis. Bertarelli and Volpino observed *Spirochaeta buccalis* and *Spirochaeta pallida* in the sputum of patients affected with heart disease. These observations were not confirmed until Aldo Castellani<sup>1</sup> reported two cases of hemorrhagic bronchitis presenting symptoms simulating those of pulmonary tuberculosis, but no tubercle bacilli could be discovered in the sputum either microscopically or by animal inoculation. In these cases large numbers of spirochetes were found in the sputum. Although Castellani pointed out that similar organisms were also found in the saliva and the superficial scrapings of the gums of his patients, he was inclined to ascribe an etiologic relationship of the spirochetes to the pulmonary disease.

From a study of his cases Castellani arrived at the conclusion that, at least in Ceylon, there is a form of bronchial and pulmonary disease caused by spirochetes. To this disease he gave the name of bronchial spirochetosis.

These findings attracted attention and soon many other observers reported similar cases seen in the tropical world. Jackson, Phalen and Kilbourne<sup>2</sup> and Weston R. Chamberlain<sup>3</sup> reported cases from the

\* From the Montefiore Home and Hospital.

1. Castellani, A.: Note on a Peculiar Form of Hemoptysis with Presence of Numerous Spirochetes in the Expectoration, *Lancet* 1:1384, 1906.

2. Phalen and Kilbourne: Report of the U. S. Army Board for the Study of Tropical Diseases made to the Surgeon-General, U. S. Army, Washington, D. C., June 30, 1909.

3. Chamberlain: The Occurrence in the Philippines of Associated Spirochetes and Fusiform Bacilli in Ulcers of the Throat (Vincent's Angina), of the Mouth and of the Skin, and in Lesions of the Lungs (Bronchial Spirochetosis), *Philippine J. Sc* 6:489, 1911.

Philippine Islands. J. A. Taylor<sup>4</sup> observed several cases of "pneumonia" among the natives of Uganda in which the causative organisms appeared to be spirochetes. He also mentions one case occurring in a European living in Uganda. J. W. Scott Macfie<sup>5</sup> reported cases observed at Accra, Gold Coast Colony, West Africa, and Frank S. Harper<sup>6</sup> noted the condition of a cook living in Tomall, Northern Territories, Gold Coast, West Africa.

That the disease is not confined to tropical countries was made apparent when Ignatz Feldmann<sup>7</sup> and K. Buday<sup>8</sup> reported several cases observed in Hungary. Buday reported many cases of pulmonary gangrene in which a careful macroscopic and microscopic study was made. The spirochetes and fusiform bacilli were found in large numbers in the gangrenous pulmonary lesions.

During the World War many causes of bronchial and pulmonary spirochetes were observed among the tropical troops brought to Western Europe. Likewise, in Europeans who had never been in the tropics, spirochetes were found in the sputum in certain cases of bronchitis and pneumonia, and of patients showing symptoms not unlike those of pulmonary tuberculosis. Thus, cases of spirochetosis bronchialis, hemorrhagic spirochetosis, etc., have been reported by G. Delamore,<sup>9</sup> Dalimier,<sup>10</sup> J. A. Thomson,<sup>11</sup> S. Fischera,<sup>12</sup> H. Violle,<sup>13</sup> F. Barbary,<sup>14</sup> P. Nolf,<sup>15</sup> P. Spehl,<sup>16</sup> and many others in France, Italy, England, Belgium, etc. G. A. Lurie,<sup>17</sup> of Chicago, reported a case observed in a Greek lady residing in Uskub, Serbia. One of us observed in the A. E. F. Hospital Center, Bazoilles, Vosges, France, two cases in Americans (white) not unlike those reported by the authors mentioned. Smears from the gangrenous pulmonary areas made at necropsy showed innumerable mouth organisms, including spirochetes. One of

4. Taylor: Bronchial Spirochetosis in Uganda, with Pneumonic Symptoms, *Ann. Trop. M. & Hyg.* **8**:13, 1914.

5. Macfie: Bronchial Spirochetosis, *J. Trop. M. & Hyg.* **18**:63, 1915.

6. Harper: Bronchial Spirochetosis, *J. Trop. M. & Hyg.* **17**:194, 1914.

7. Feldmann: Beitrag zu den durch *Bacillus fusiformis* und *Spirillum dentium* herangerufenen Infektionen mit besonderer Berücksichtigung der Eiterungen, *Wiener. klin. Wchnschr.* **19**:695, 1906.

8. Buday: Histologische Untersuchungen über die Entstehungsweise der Lungengangrän, *Beitr. z. path. Anat. u. z. allg. Path.* **48**:700, 1910.

9. Delamore: *Bull. et mem. Soc. méd. d. hôp. de Par.* **43**:526, 1919.

10. Dalimier: *Presse méd.* **27**:124, 1919.

11. Thomson: Pulmonary Spirochetosis, *Brit. M. J.* **2**:775, 1919.

12. Fischera: *Riforma med.* **34**:384, 1918.

13. Violle: *Bull. de l'Acad. de méd., Par.* **79**:429, 1918.

14. Barbary: *Bull. de l'Acad. de méd., Par.* **79**:461, 1918.

15. Nolf and Spehl: *Arch. méd. Belges* **71**:1, 1918.

16. Nolf, P.: Fetid Spirillar Bronchitis and Pulmonary Gangrene, *Arch. Int. Med.* **25**:429 (April) 1920.

17. Lurie, G. A.: Note on Castellani's Broncho-Spirochetosis, *J. Trop. Med. & Hyg.* **18**:269, 1915.



these patients had marked dental caries, and smears from the material in the cavities likewise showed many mouth organisms including spirochetes.

It is noteworthy that even before these reports were made, J. H. Rothwell<sup>18</sup> reported two cases of "bronchial Vincent's angina" with symptoms and signs simulating pneumonia, but in which the sputum was found to be full of spirillae and fusiform bacilli.

More recently Ralph R. Mellon<sup>19</sup> reported a series of cases of whooping cough, pneumonia and empyema from Rochester, N. Y., in



Fig. 1.—Right lung: Extensive bronchopneumonia with gangrenous ulceration in right lower lobe.

which fusiform bacilli were discovered in the sputum. A. N. Sinclair<sup>20</sup> also found in the Philippine Islands numerous cases of pulmonary hemorrhage of tuberculous origin, in which Vincent's spirochetes, or fusiform bacilli were discovered in the sputum. It is his opinion that the presence of fusiform bacilli predisposes to hemoptysis

18. Rothwell: Bronchial Vincent's Angina, *J. A. M. A.* **54**:1867 (June 4) 1910.

19. Mellon: A Clinical and Bacteriological Study of Fusiform Bacillus Infection, *New York State J. M.* **20**:187, 1920.

20. Sinclair: Vincent's Spirochetes and Hemorrhage in Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **4**:201, 1920.

in tuberculous individuals, and that hemorrhage only rarely occurs in incipient cases unless they are present.

The following case of pneumonia with gangrenous ulceration, apparently caused by spirochetes, observed at the Montefiore Hospital, is believed to be the first reported in New York:

#### REPORT OF CASE

M. S. (No. 027757), aged 33, native of Russia, six years in the United States; tailor; admitted April 19, 1920, as a case of pulmonary tuberculosis.

Symptoms on admission: Fever, reaching 105 F., of a continuous type; severe, incessant cough, copious expectoration of foul smelling, greenish mate-

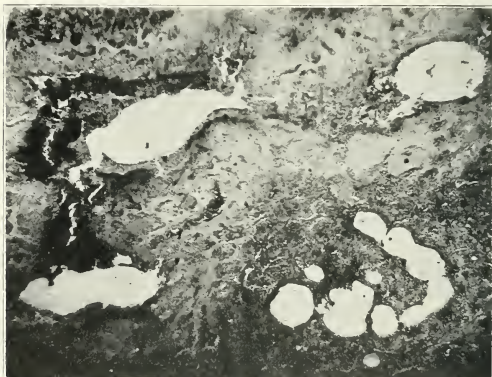


Fig. 2.—Pneumonia with associated gangrenous ulceration. Low power.

rial, at times bloody; dyspnea, cyanosis, prostration. The mental state of the patient precluded obtaining a clear cut and reliable history of the case, but combining the data elicited from him with those given by his friends who visited him at the hospital, we find that his family and personal past history present no conditions which may have had any bearing on his present state. He had been married for eight years, had two children, both alive and well, and had worked at his trade, tailoring, without interruption due to illness, till March 15, 1919, when he began to cough and expectorate. This cough, however, was at the beginning so slight, that he believed it to be due to excessive smoking and he paid little attention to it.

During the first week of April, he was suddenly seized with vomiting, followed by fever and prostration. A physician who examined him at that time informed him that "weak lungs" were responsible for his trouble and advised a trip to the mountains. The severity of the disease prevented his leaving the city. The frequent chills, high fever and sweats became very marked and

he was referred to the Montmore Hospital with a diagnosis of acute progressive pulmonary tuberculosis.

On admission it was felt that we were dealing with a case of gangrene of the lungs. The foul, sharp, penetrating odor of the breath and expectoration pointed in this direction; the high fever, the sweats and the prostration gave support to this provisional diagnosis. Physical exploration of the chest revealed a suspended area of flatness in the middle of the right side of the chest; this flatness was most marked over the lower two-thirds of the interscapular space. On auscultation the breath sounds were found feeble, hardly audible over the flat area, while over the upper lobe of the right lung, medium sized, moist râles were heard; over the right base, in the axillary space, a soft friction sound was made out. There were also signs of fluid in the left pleural cavity: flatness, feeble breath sounds, abolition of vocal fremitus, dullness



Fig. 3.—Smear from gums (Fontana stain) high power. Spirochetes and other organisms.

in Traube's space, etc. These signs elicited on physical examination of the chest suggested either an interlobar empyema which had broken through a bronchus, a pulmonary abscess which may thus have originated, or gangrene of the right lung. A roentgenogram confirmed the findings of physical exploration. A large, somewhat round, shadow, occupying the middle third of the right lung, was disclosed. The rest of the lung showed evidences of hyperaeration.

Of the laboratory findings, the following are of interest: Blood—hemoglobin, 70 per cent.; leukocytes, 21,000; lymphocytes, 18 per cent.; polymorphonuclears, 80 per cent. Wassermann reaction (blood) negative; urea N 13.7 per 100 c.c.; creatinin, 4.3 per 100 c.c. Urine: acid; sp. gr. 1.022; slight amount of indican; no albumin; no sugar;

Ehrlich's diazo reaction negative; no casts; no tubercle bacilli. Repeated search also failed to disclose tubercle bacilli in the sputum.

Correlating the history with the physical and roentgenographic signs it appeared that the process was not an interlobar empyema. There was no history of an acute onset with pain in the chest, fever, etc., nor has the temperature declined sufficiently to indicate that empyema broke through a bronchus and was being drained. The fetid odor of the expectoration also spoke against an interlobar abscess; there was no history of an acute pulmonary disease such as pneumonia, preceding it. As soon as the patient began to expectorate, the sputum

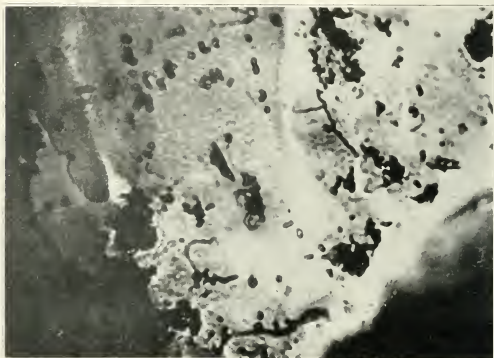


Fig. 4.—Gangrenous lung (Fontana stain), high power. Spirochetes and other organisms.

had the sharp penetrating odor characteristic of gangrene. A foreign body in a bronchus was thought of, but the history, symptomatology and the roentgenogram spoke against it.

The history, symptomatology, physical and roentgenographic signs, combined with the laboratory findings, were thus all against a diagnosis of tuberculosis. As has already been stated, an interlobar empyema was also excluded. The slow onset, the absence of a history of acute pulmonary disease, or operation on the tonsils, etc., also spoke against pulmonary abscess. Furthermore, the expectorated material had the intensely penetrating odor characteristic of gangrene of the lung.

The sputum was then again sent to the laboratory with a request that a careful search be made for spirochetes. With the Fontana

stain, the presence of fusiform bacilli and spirochetes was readily demonstrated. Inasmuch as these organisms are very often found on the gums of healthy individuals, and especially the gums of those who suffer from pyorrhea alveolaris, the sputum was carefully washed, and it was found to contain numerous spirochetes. The material scraped from the gums was then examined and many spirochetes, of the morphology of *Spirocheta microdentium* and *S. macrodentium* were found; some had the morphology of the *Spirochacta bronchialis* of Castellani. A few had an appearance not unlike that of *Spirochacta pallida*.

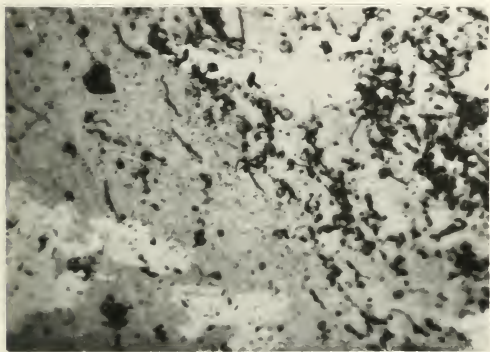


Fig. 5.—Smear from gangrenous lung (Fontana stain), high power. Spirochetes and other organisms.

The usual symptomatic treatment apparently had no effect on the progress of the disease. The fever remained high, between 103 and 104 F.; cerebral symptoms made their appearance and the prostration remained severe. The foul odor of the expectoration and the weakness of the patient increased. Reports have shown that in some cases of abscess and gangrene of the lung, artificial pneumothorax has proven of value, though in the experience of one of us, it has never been a success in this class of cases. On entering the right pleural cavity with the pneumothorax needle May 5 we found excellent negative pressure with respiratory oscillations and allowed 400 c.c. of air to enter. The intrapleural pressure remained minus 10 after the initial inflation.

No improvement was noted in the general condition of the patient after the pneumothorax was induced. The fever remained high, the prostration continued, and the weakness increased. May 6, the cerebral symptoms became accentuated, the patient died at 4:30, manifesting intense dyspnea and cyanosis.

For special reasons a complete necropsy could not be made; only the thoracic and abdominal viscera were removed for examination.

The lungs showed extensive coalescing lobular and bronchopneumonia of both upper lobes and the right middle lobe. In the right lower lobe, associated with the consolidated lung, there was extensive gangrenous ulceration, the ulcerated areas varying in size from several millimeters to a cavity 4 cm. in diameter.

Microscopically, the picture was that of extensive lobular and bronchopneumonic exudation with numerous areas of necrosis and gangrene. With Fontana and MacCallum stains, spirochetes and fusiform bacilli were observed in large numbers in the necrotic and gangrenous areas. The following is an abstract of the necropsy protocol:

#### NECROPSY PROTOCOL

The larynx and upper part of the trachea were not removed. The lower portion of the trachea and right bronchus show an intensely injected, swollen mucosa. In the lumen, there is a considerable amount of mucopurulent material. In the left pleural sac, several hundred c.c. of thin, blood tinged fluid were found.

**Lungs:** All lobes much more voluminous than usual. The upper lobes cushiony, soggy; middle and lower lobes soggy, solid. The pleura is thickened over the upper lobes and over the posterior portions of the lower lobes. There are sheetlike, fibrous tags in these areas. There is some fibrinous exudate over the lateral and median portions of both lower lobes. Glands at the hilum enlarged, pulpy, edematous, injected, pigmented. On section of the upper lobes, a moist, dark red surface presents. The tissue is apparently congested and edematous. There is no definite consolidation. There is a considerable amount of thin fluid in the air sacs. The bronchial branches show an injected, swollen mucosa, overlaid by blood tinged, mucopurulent material. Right middle lobe on section, shows extensive consolidation, the patches small, several millimeters to one centimeter in diameter, almost adjoining one another throughout the lobe. These areas are soft, yellowish, almost purulent. They are, however, considerably more coherent than abscesses. Both lower lobes on section show extensive, patchy consolidation, the patches almost adjoining each other throughout the lobes. This is especially true in the posterior portions. The patches in these lobes also vary in size from several millimeters to one centimeter. They vary in color from reddish yellow to dark green. The latter color is especially marked in the right lower lobe. In addition, many of the dark green, consolidated patches show central ulceration. The cavities vary in size from a few millimeters to four centimeters in diameter. The large cavity is present in the upper anterior portion of the right lower lobe, well below and median to the apical portion. There is no sharp reaction zone about the cavities. They are all surrounded by greenish, consolidated lung. Within the cavities, there is thin, greenish, necrotic material. The ulceration in the left lower lobe is much less advanced than in the right lower. The bronchial tree throughout, shows beginning calcification of the cartilages. The mucosa is swollen, injected, overlaid by mucopurulent material. In places, espe-

cially in the right lower lobe, the mucosa has a greenish tint. The lungs have an intense, penetrating, disagreeable odor.

Smears from the yellow and green consolidated areas and cavities show innumerable, gram-negative spirillae and spirochetes resembling *Spirochaeta microdentium*, *S. macrodentium* and *S. refringens*, the latter present in small numbers. Throughout the smears there are also innumerable gram-negative bacilli. Some of these are small, resembling *Bacillus influenzae*; others are larger. Some of the larger gram-negative bacilli have a safety-pin appearance, resembling colon bacilli. In addition, there are a large number of rounded, gram-negative cocci and some diplococci. In the smears the following gram-positive organisms were noted: innumerable diphtheroids, many rounded cocci, rounded and lancet shaped diplococci, scattered small chains of rounded cocci, also scattered, straight and curved, beaded bacilli with tapering ends about the size of gas bacilli and somewhat smaller.

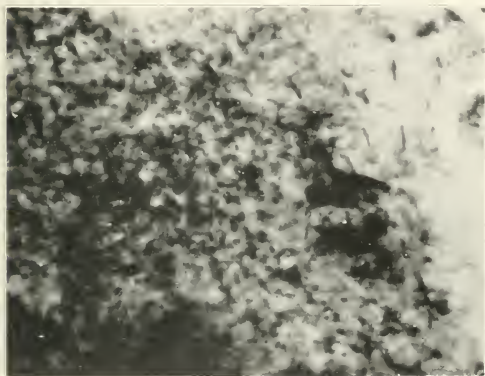


Fig. 95.—Section of gangrenous lung (MacCallum stain), high power. Fusiform bacilli and other organisms.

**Microscopic Sections:** Section 1 shows on gross inspection a number of circumscribed areas from one to several millimeters in diameter with pink periphery and bluish center. Alveoli in general apparently filled. Under low power, the circumscribed areas mentioned above are seen to be composed of a zone of necrotic pink stained lung tissue and exudate, the central portions bluish, consisting of masses of organisms. There are many of these necrotic areas in the section; in places they adjoin one another; in places they are discrete and vary in size from that of a glomerulus to several millimeters in diameter. In addition to these areas, the alveoli throughout the section in general are filled with exudate composed of swollen alveolar cells and amorphous pink stained material and a few wandering cells. The alveolar walls, in general, show swollen epithelial cells with blood vessels moderately engorged. In places, the alveoli are filled in great part by red blood cells. Portions of the pleura in the section are swollen, distended by amorphous



pink stained material, red blood cells and scattered wandering cells. There is a small amount of fibrin present. In places there is definite beginning organization of the exudate.

Section 4 shows in addition to circumscribed necrotic areas with masses of blue stained organisms, the adjoining alveoli filled with pus cells and mononuclear cells, the nuclei of the majority of these being deeply stained (pyknotic). External to the alveoli filled with pus cells, are alveoli filled with large mononuclear cells, some containing blood pigment, some pus cells, some red blood cells and some amorphous pink stained material. The pulmonary vessels throughout are engorged. In this section there are numerous groups of alveoli filled with exudate rich in polymorphonuclears; in places there is definite necrosis of the exudate. In places there are circumscribed masses of blue stained organisms. There are scattered bronchial branches filled with necrotic exudate containing blue stained organisms, the epithelium of these bronchial branches is almost homogeneously pink stained, the nuclei being barely visible. Throughout all coats of bronchial branches the blood vessels are engorged. There is apparently considerable thickening due to the presence of granulation tissue. In places, in the section the alveoli contain in great part amorphous pink stained material (serum) and scattered, desquamated cells. In places, the exudate is present in the peribronchial alveoli, in places the exudate is apparently lobular in distribution and varies in proportion of serum, large phagocytic mononuclear cells, pus cells and red blood cells. In places, there is definite organization of the exudate; in other places there is necrosis and ulceration associated with blue stained masses of organisms.

Section 5 shows a wall of a large cavity composed of amorphous pink stained necrotic material in the innermost zone, external to which there is granulation tissue composed of numerous engorged capillaries and fairly densely layered connective tissue cells. In places, the connective tissue cells are loosely connected. In places, there are numerous plasma cells in the granulation tissue. External to this zone there are numerous, somewhat collapsed alveoli filled with exudate, varying in character, as described above. In this section also there are fair sized bronchial branches with greatly thickened walls, due to granulation tissue.

Sections of the lung stained by Fontana method show in the necrotic areas a considerable number of spirochetes resembling *Spirochaeta macrodentium* and *S. microdentium*. With this stain, innumerable other organisms are observed in the necrotic and consolidated portions. Sections stained by MacCallum's stain show in the consolidated and necrotic areas innumerable gram-positive organisms including gram-positive bacilli, some of these having the morphology of diphtheroids; gram-negative bacilli, some having the morphology of influenza bacilli, also gram-positive and gram-negative cocci. There are also many large slightly curved gram-positive bacilli, not unlike the fusiform bacilli of Vincent's angina. The spirochetes are poorly stained by this method. With this stain the predominant organism is the somewhat gram-positive bacillus.

#### DISCUSSION

The presence of numerous spirochetes in the gangrenous portions of the lung in the case reported, suggests their etiologic relationship to the lesion. It is probable that the spirochetes responsible for the gangrene in this case are of the type Castellani calls *Spirochaeta bronchialis*. While, of course, there are present in the lesions numerous mouth organisms, the overwhelming number of the spirochetes, as well as the study of their location in the diseased area, and the cellular reaction to their presence, compels the conclusion that the predominantly gangrenous lesions are to be directly attributed to the spirochetes.



## THE SIGNIFICANCE OF THE ACIDOSIS OF METHYL ALCOHOL POISONING\*

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The increase in the number of cases of poisoning by methyl alcohol that has occurred recently renders particularly interesting the report of the favorable results obtained by Harrop and Benedict<sup>1</sup> in the treatment of a case of such poisoning with sodium bicarbonate. The rationale of this treatment depends on the fact first demonstrated by Król<sup>2</sup> that there is an abnormal excretion of acid bodies in the urine following the ingestion of methyl alcohol. Since Pohl<sup>3</sup> had previously shown that methyl alcohol is slowly and incompletely oxidized in the body, a considerable proportion of that administered being excreted in the shape of formic acid, it was believed that this formic acid was responsible for the "acidosis." Król, however, found that the formic acid accounted for only a small part of the ammonia of the urine, indicating that other organic acids were excreted in abnormal amounts. Tyson and Schoenberg<sup>4</sup> also found that there was an acidosis, as determined by the decreased titratable alkalinity of the body fluids, when methyl alcohol was administered by inhalation. While the suggestion has been made that the acidosis might be an important factor in producing the poisonous action of methyl alcohol, apparently Harrop and Benedict were the first to treat a patient on this assumption. In the case reported by these authors there was a definite reduction in the reserve alkali and there was also the characteristic air hunger.

It is now known that a reduction of the reserve alkali of the blood occurs in a variety of pathologic states, but the exact significance of this reduction is not clearly understood. There is evidence that strongly suggests that the disturbance of the acid-base balance may, in itself, cause definite anatomic changes. Thus, Graham, studying delayed

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\* From the laboratory of pharmacology, Medical College of Virginia.

1. Harrop and Benedict: Acute Methyl Alcohol Poisoning Associated with Acidosis, *J. A. M. A.* **74**:25 (Jan. 3) 1920.

2. Król: Cited by Harrop and Benedict.<sup>1</sup>

3. Pohl: Ueber die Oxydation des Methyl- und Aethylalkohols im Tierkörper *Arch. f. exper. Path. u. Pharmacol.* **31**:281, 1892.

4. Tyson and Schoenberg: Experimental Researches in Methyl Alcohol Inhalation, *J. A. M. A.* **63**:915 (Sept. 12) 1914.

5. Graham: Late Poisoning with Chloroform and Other Alkyl Halides in Relationship to the Halogen Acids Formed by Their Chemical Dissociation, *J. Exper. M.* **22**:48, 1915; Sodium Carbonate in Chloroform Poisoning, *Arch. Int. Med.* **25**:575 (May) 1920.

chloroform poisoning, finds that sodium carbonate administration protects against the lesions seen in the liver, and from this and other considerations, he believes that the lesions are caused by the production of hydrochloric acid from a splitting of the chloroform in the body. MacNider<sup>6</sup> in a similar manner finds that the carbonate lessens or prevents the kidney injury that is seen following the administration of uranium nitrate to dogs, and suggests the possibility that these renal injuries are due to the formation of acids as a result of a depressant action the uranium exerts on oxidative processes in the cell. The discovery of a reduction of the alkali reserve in the patient under their care is probably justification for the institution of alkali therapy by Harrop and Benedict, and the results are sufficiently striking to give encouragement. However, one case is far from conclusive, so it was deemed advisable to endeavor to ascertain by animal experimentation the importance of the rôle of acidosis in the production of the symptoms of methyl alcohol poisoning and the benefits to be derived by the administration of sodium bicarbonate.

As was pointed out by Joffroy and Serveaux,<sup>7</sup> Pohl,<sup>8</sup> Hunt<sup>8</sup> and others, poisoning by wood alcohol may be of either the chronic or acute type. Owing to the incomplete oxidation and slow excretion of this alcohol, there is a decided tendency to cumulation, so that small, nontoxic doses given repeatedly will lead eventually to severe or fatal poisoning. This type of case presents a hopeless outlook from the beginning, because the damage has already been done before the patient comes under observation. On the other hand, where poisoning has followed the ingestion of a single large dose or of a few repeated large doses, it is probable that the outcome may be influenced by treatment, for here the attempt may be made to neutralize the toxic agent or hasten its elimination before irreparable damage has been done. Many of the recent cases were of this second type, Harrop and Benedict's being illustrative. Therefore, we have made the attempt to determine the acute toxicity of methyl alcohol for dogs; to ascertain whether an acidosis occurs in animals so poisoned, and to estimate the value of alkaline treatment under such conditions.

According to Hunt,<sup>8</sup> the toxicity of the purest available methyl alcohol is closely approximated by that of ordinary "Columbian spirits" and similar commercial preparations. Nevertheless, we have used a

6. MacNider: The Inhibition of the Toxicity of Uranium Nitrate by Sodium Carbonate, and the Protection of the Kidney Acutely Nephropathic from Uranium from the Toxic Action of an Anesthetic by Sodium Carbonate, *J. Exper. M.* **23**:171, 1916.

7. Joffroy and Serveaux: Mesuration de la toxicité expérimentale et de la toxicité vraie de l'alcool méthylique, *Arch. de méd. exper.* **8**:473, 1896.

8. Hunt: The Toxicity of Methyl Alcohol, *Bull. Johns Hopkins Hosp.* **13**:213, 1902.

high grade of methyl alcohol, marketed by Merck under the title of Reagent Alcohol Methylic, and, according to the label on the bottles, having the following maximum limit of foreign substances: Non-volatile matter, 0.0020 per cent.; acetone, 0.0150 per cent.; ethyl alcohol, 1.0000 per cent.; empyreumatic substances, 0.0000 per cent.; aldehyds, 0.0000 per cent.; substances oxidizable by permanganate, 0.0000 per cent.; chloroform, 0.0100 per cent.

Dogs were used as experimental animals, the drug being given undiluted either subcutaneously or orally. The injections were made at room temperature from a buret connected with a hypodermic needle for the subcutaneous injections or with a catheter used as a stomach tube when oral administration was practiced. In the latter case, the dogs received a preliminary injection of 10 mg. morphin sulphate per kilogram of body weight in order to prevent emesis from the irritant action of the alcohol in the stomach.

To detect the existence of an acidosis, the method of Van Slyke and Cullen for determining the carbon dioxid combining power of the plasma was used.<sup>9</sup> Blood was generally drawn from the external jugular vein; occasionally from the femoral; and, in one instance, from the heart. It was found convenient to employ a 10 c.c. syringe, coated with petrolatum. On securing approximately 10 c.c. of blood, the needle was removed and the syringe connected with a short piece of oiled rubber tubing, through which the blood was forced into a centrifuge tube, containing a small amount of liquid petrolatum and a few drops of a saturated solution of potassium oxalate. By means of the tube, blood and oxalate were well mixed. We could not detect that these slight modifications exerted any influence on the values obtained, and clotting was less likely to occur.

With sufficiently large doses of the alcohol, the usual intoxication was produced with its slow onset and persistent coma. Twitching of the facial muscles invariably occurred, but we did not observe actual convulsions from any dose of the alcohol. The subcutaneous injection of the strong alcohol caused some slight temporary discomfort, but this soon passed off. Following either method of administration, after the onset of the coma, many of the dogs cried out constantly, their cries becoming much louder if they were handled in any way.

When alcohol is injected subcutaneously, it is seen that there exists considerable variation in the resistance of different animals to the poisonous action. Thus, one dog died following the injection of 5 c.c. alcohol per kilogram of body weight and one dog died following a dose of 6 c.c. per kilogram of body weight, while two dogs that were

9. Van Slyke and Cullen: The Bicarbonate Concentration of the Blood Plasma, etc. *J. Biol. Chem.* **30**:239 1917

given 7 c.c. alcohol per kilogram of body weight survived. A dose of 8 c.c. was fatal to three dogs. Other investigators have placed the lethal subcutaneous dose for dogs at a slightly higher figure; Dujardin-Beaumetz and Audigé<sup>10</sup> stating it to be about 7 gm. per kilogram, while Joffroy and Serveaux<sup>7</sup> place the lethal intramuscular dose for dogs at about 9 c.c.

Our results are given in Table 1.

TABLE 1.—RESULTS OF SUBCUTANEOUS INJECTION OF METHYL ALCOHOL

Number of Experiment	Weight in Kg.	Dose of Alcohol in C.c. per Kg.	Result
1	16.1	4	Survived
1	6.1	5	Died
2	14.1	6	Died
3	9.5	7	Recovered
5-A	12.95	7	Recovered
-	8.18	8	Died
8	5.1	8	Died
9	7.16	8	Died

When the alcohol is given orally, similar individual variations are encountered. Thus, it is found that one dog succumbed to a dose of 5 c.c. per kilogram; two dogs died from a dose of 6 c.c. per kilogram, while two of eight survived a dose of 8 c.c. per kilogram. Therefore, even this last dose cannot be said to be the surely fatal dose, but, at the time these experiments were carried out, the majority of dogs succumbed to it. These results are tabulated in Table 2.

TABLE 2.—RESULTS FROM ORAL ADMINISTRATION OF METHYL ALCOHOL TO DOGS

Number of Experiment	Weight of Dog in Kg.	Alcohol, C.c. per Kg.	Result
90	4.66	4	Recovered
19	9.8	4	Recovered
91	3.86	5	Died in less than 140 hours
20	7.3	6	Survived
87	4.96	6	Died in 53 hours
88	6.93	6	Died between 120 and 130 hours
50	17.7	8	Recovered
86	10.08	8	Recovered
39	7.5	8	Died in less than 60 hours
28	3.4	8	Died in less than 48 hours
29	7.0	8	Died in less than 120 hours
89	7.27	8	Died in less than 40 hours
13	12.5	8	Died in less than 72 hours
55	8.18	8	Died in less than 16 hours
25	4.95	8	Died between 48 and 60 hours

In dogs showing severe symptoms of poisoning after either the subcutaneous or oral administration of methyl alcohol, there is usually a marked reduction in the plasma bicarbonate carbon dioxide combining power. This is well illustrated by the results obtained with Dogs 1 and

10. Dujardin-Beaumetz and Audigé: Cited by Hunt.<sup>4</sup>

2. The alcohol was injected subcutaneously into these two dogs, the doses being 5 and 6 c.c. per kilogram, respectively. Death ensued in both instances. Prior to the injection of the alcohol, the Van Slyke test gave a plasma bicarbonate value of 56 and 58 c.c. of carbon dioxide per 100 c.c. of blood, respectively. Eighteen hours later, these values had fallen to 43 and 45 c.c.; while, at the end of forty-eight hours, the figures were 26 and 24 c.c. On the other hand, Dog 3 received a subcutaneous dose of 7 c.c. of alcohol per kilogram, but failed to develop the severe intoxication seen in the other dogs; in keeping with which, the plasma bicarbonate carbon dioxide did not fall below 33 c.c. per 100 c.c. and soon returned toward normal. This last animal recovered completely without treatment. Figure 1 represents graphically the changes seen in the reserve alkali in these three dogs.

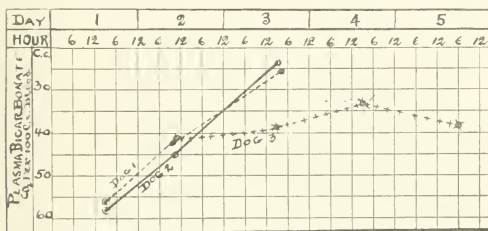


Fig. 1. Changes in reserve alkali in three dogs following subcutaneous injection of alcohol. Dog 1 received 5 c.c. methyl alcohol per kg., died. Dog 2, 6 c.c. alcohol per kg., died. Dog 3, 7 c.c. alcohol per kg., lived.

In a similar manner, the intensity of the symptoms and the degree of acidosis run parallel in Dogs 90 and 91, to whom oral doses of 4 and 5 c.c. per kilogram, respectively, were given. Dog 90 was not seriously affected, and there was a relatively small reduction in the plasma bicarbonate carbon dioxide. On the other hand, dog 91 was very sick, dying on the fifth day, and her reserve alkali was correspondingly reduced. Figure 2 illustrates the results seen.

Such observations as these give additional support to the view that the acidosis plays an etiologic rôle in the production of the symptoms following poisoning by methyl alcohol and serves as justification for the opinion that alkaline therapy is indicated here. We have obtained evidence, however, which leads us to believe that:

1. In dogs poisoned with methyl alcohol, the severity of the intoxication is, at times, entirely at variance with the degree of acidosis.

2. The intravenous administration of alkali is a procedure by no means devoid of danger.

3. Alkali, in the form of sodium bicarbonate, has, in itself, little or no influence on the course of poisoning.

#### PROTOCOL OF EXPERIMENTS

The following experiments may be cited in support of the first point.

EXPERIMENT 23.—April 30, 1920. Female poodle, weight, 4.95 kg.

3:34 p. m., received 10 mg. morphin sulphate per kilogram subcutaneously.

4:30 p. m., received 10 c.c. methyl alcohol per kilogram orally.

May 1, 9:30 a. m.: Very deeply unconscious and unresponsive to all ordinary stimuli.

11:49 a. m.: Condition about the same; blood from jugular gives plasma bicarbonate carbon dioxid, 61.3 c.c.

Dog died the night of May 2 without any improvement in symptoms.

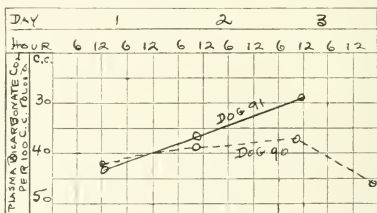


Fig. 2.—Two dogs were given oral doses of methyl alcohol. Dog 90 received 4 c.c. per kg. and lived. Dog 91 received 5 c.c. per kg., and died.

Here is an animal that received a dose of methyl alcohol sufficient to cause evidences of severe intoxication and, eventually, death, yet at the end of nineteen hours, when the depression was profound, there was no reduction in the reserve alkali of the blood. Even more striking, however, is the next experiment.

EXPERIMENT 16.—April 30, 1920. Female fox terrier, weight 4.8 kg.

10:52 a. m., received 10 mg. morphin sulphate per kilogram subcutaneously.

11:25 a. m., received 10 c.c. methyl alcohol per kilogram orally.

4:40 p. m.: Deeply unconscious. Blood carbon dioxid, 66.1 c.c.

4:52 p. m.: Respiration ceases; heart beats a few times and then stops.

Twelve minutes before a fatal termination, the plasma bicarbonate carbon dioxid was quite high. The next experiment shows that a reduction of the alkali reserve does not always lead to or accompany severe symptoms.

EXPERIMENT 89. July 24, 1920. Black female mongrel, weight, 10.8 kg.

11:44 a. m., received 10 mg. morphin sulphate per kilogram subcutaneously.

12:02 p. m.: Blood carbon dioxid, 43.9 c.c.

12:18 p. m., received 8 c.c. methyl alcohol per kilogram orally.

July 25, 10 a. m.: Only after repeated efforts is dog able to rise to her feet, when she staggers around, almost falling. Blood carbon dioxid, 33.2 c.c.

July 28, 9:43 a. m.: Dog practically normal. Eats greedily and runs without the least evidence of unsteadiness. Blood carbon dioxid, 29.6 c.c.

July 31, 9 a. m.: Dog seems fully normal.

July 25, the dog seemed to be severely poisoned, the plasma bicarbonate carbon dioxid, in keeping with this, being reduced almost 25 per cent. Three days later, however, the visible evidences of intoxication had entirely disappeared, in spite of the fact that the plasma bicarbonate carbon dioxid had undergone a still further reduction. It is interesting to chart the results obtained in Experiment 89 and compare them with those obtained in Dog 91. In this dog, there was

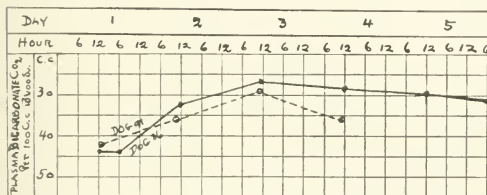


Fig. 3.—Comparison of results in Dogs 91 and 86, who were given 5 and 8 c.c. methyl alcohol, respectively, per kg. Dog 91 died. Dog 86 lived.

a steady increase in the severity of the symptoms, the dog dying on the fifth day, but, accompanying this, there was a rise in the reserve alkali. This comparison is given in Figure 3.

Sodium bicarbonate is the salt generally employed in the treatment of acidosis. While usually given by mouth or rectum, not infrequently it is injected intravenously, especially when there seems to be urgent need or when, as in Harrop and Benedict's case, vomiting occurred after its oral administration. There does not seem to be any definite rule as to the strength of solution to be employed, or as to the amount that may be injected. Harrop and Benedict used a 5 per cent. solution, and in a number of instances in the literature mention is made of the use of a solution of this strength in other conditions than the acidosis of methyl alcohol poisoning. The amount given varies greatly. Not infrequently as much as a liter of a 5 per cent. solution is injected intravenously in adults, but Harrop and Benedict used only 500 c.c.

as their maximum single injection. The weight of their patient is not stated, but, assuming her to have been of average size, this would mean a dose of from 8 to 10 c.c. per kilogram.

In most of our early experiments, a solution of 5 per cent. strength was used. This was made by dissolving the bicarbonate in distilled water or in tap water; boiling the solution for a few minutes, allowing it to cool and then passing carbon dioxide through it for about thirty minutes. Twice, a solution of 10 per cent. strength was used. Using no anesthetic, the vein was not exposed, the injections of the bicarbonate solution being made through the skin into the jugular vein as a rule, occasionally into an ear vein. Naturally, it was of importance to avoid injury to the vessel as much as possible, because the production of a hematoma rendered the vein of no use for subsequent injections. Impressed by this, we attempted to make these earlier injections as rapidly as practicable, using a 19 gage needle and exerting pressure on the fluid in the transfusion flask, so that the total amount was introduced in from three to eight minutes. The results obtained by this method of treatment are given in Table 3.

TABLE 3.—RESULTS OF TREATMENT WITH 5 AND 10 PER CENT. SODIUM BICARBONATE SOLUTION; RAPID INJECTION

Number of Experiment	Weight in Kg.	Dose of Alcohol in C.c. per Kg.	Strength of Solution of Sodium Bicarbonate	Result
5*	14.0	7	5%	Died
10*	17.0	8	10%	Died
11*	21.8	8	10%	Died
12*	23.2	8	5%	Died
27	8.2	8	5%	Died
32	16.6	8	5%	Died
35	6.1	8	5%	Died

\* In these dogs, the alcohol was injected subcutaneously; in the others it was given orally.

An experience such as this is not likely to render one enthusiastic over the alkaline treatment, but an analysis of the experiments discloses the probability that death was due in every instance to a toxic action of the bicarbonate and not due to the alcohol. Of the seven dogs, six died immediately after the injection of the solution, and all showed such striking symptoms as a result of this injection, that it is scarcely conceivable that death was due to any other cause. This is well shown in the following experiment.

EXPERIMENT 10.—April 26, 1920. Black and white male hound; weight, 17 kg.

5:26 p. m., received 8 c.c. methyl alcohol per kilogram injected subcutaneously.

5:55-5:58 p. m., received 10 c.c. per kg. of a 5 per cent. sodium bicarbonate solution injected into the jugular. No untoward symptoms.

April 27, 10:06 a. m.: Deeply unconscious. Blood carbon dioxide, 62 c.c.



11:50-11:54 a. m.: 5 c.c. per kilogram of a 10 per cent. sodium bicarbonate solution injected into the jugular. No untoward symptoms.

April 28, 11:10 a. m.: Condition about the same. Blood carbon dioxid, 52.6 c.c.

4:12-4:14 p. m.: 4 c.c. per kilogram of a 10 per cent. sodium bicarbonate solution injected into the jugular. Immediate stiffening of limbs and arching of back; respiration deepened and quickened; heart pulsations not palpable; cardiac massage and artificial respiration ineffectual.

Of the remaining six dogs, five died immediately on receiving the sodium bicarbonate injections; one developed convulsions following the injection but breathed spontaneously after ten minutes of cardiac massage and artificial respiration, only to die the following night. Convulsions did not occur invariably, however, for three of the dogs died without manifesting them. It is true, that this rapid method of injecting sodium bicarbonate intravenously should never be practiced clinically, but our results serve to emphasize anew the danger that may attend the intravenous injection of an alkali. That convulsions and death may follow this procedure in dogs has already been pointed out by MacCallum, Lintz, Vermilye, Leggett and Boas;<sup>11</sup> and the clinical occurrence of similar manifestations has been described by Blum,<sup>12</sup> Howland and Marriott<sup>13</sup> and Harrop.<sup>14</sup> It would seem natural to assume that the production of an "alkalosis," to use the term of Wilson and his associates,<sup>15</sup> is responsible for the symptoms, but there are certain points which are not in harmony with such an hypothesis. Thus, in our experiments, we found that the acid-base balance of the blood did not serve as a guide to the amount of bicarbonate which would be tolerated. Dog 10 illustrates this, for April 27, with a plasma bicarbonate carbon dioxid of 62 c.c. per 100 c.c. of blood, he suffered no apparent harm from the injection of 5 c.c. per kilogram of a 10 per cent. solution of sodium bicarbonate into the jugular vein; while, on the following day, with a reduction of the plasma bicarbonate carbon dioxid to 52.6 c.c., 4 c.c. per kilogram proved fatal. Likewise, Dog 11 withstood safely an intravenous injection of 5 c.c. per kilogram of a 10 per cent. solution of sodium bicarbonate, the plasma bicarbonate carbon dioxid being 59.4 c.c. per 100 c.c.; but on the following day,

11. MacCallum, Lintz, Vermilye, Leggett and Boas: The Effect of Pyloric Obstruction in Relation to Gastric Tetany, *Bull. Johns Hopkins Hosp.* **31**:1, 1920.

12. Blum: Les dangers des injections intraveineuses alcalines, *Semaine méd.* **36**:433, 1911.

13. Howland and Marriott: Observations upon the Calcium Content of the Blood in Infantile Tetany and upon the Effect of Treatment by Calcium, *Quart. J. Med.* **2**:289, 1917.

14. Harrop: The Production of Tetany by the Intravenous Infusion of Sodium Bicarbonate, *Bull. Johns Hopkins Hosp.* **30**:62, 1919.

15. Wilson, Stearns and Janney: The Effect of Acid Administration on Parathyroid Tetany, *J. Biol. Chem.* **21**:169, 1915.

with a plasma bicarbonate carbon dioxid reduced to 57.4 c.c., a repetition of the injection caused death.

MacCallum and his collaborators observed an increase in the plasma bicarbonate carbon dioxid as high as 119 c.c., without the appearance of convulsions, but the injection was made slowly and they probably used an anesthetic. Collip and Backus<sup>16</sup> also injected large amounts of sodium bicarbonate solution into the veins of dogs without the appearance of convulsions, but the same factors were present here as in the experiments of MacCallum. Blum states that the occurrence of the symptoms may be delayed some hours after the completion of the injection of the alkali, which is hardly in accordance with the view that they are due to a sudden disturbance in the acid-base equilibrium. The suggestion of Blum that the convulsions are the result of a toxic action of the sodium ion seems improbable, because the more readily ionizable sodium chlorid does not produce convulsions when injected in this manner in the form of a 5 per cent. solution, as judged by a single experiment.

To obtain information regarding the third point, namely, that sodium bicarbonate administered in such a way as not to cause the death of the animal does not markedly influence the course of the poisoning, two methods of procedure were adopted; first, the oral method of administering the bicarbonate, and second, the intravenous injection at so slow a rate that a fatal outcome is avoided.

To determine the value of the orally administered alkali, four dogs were given 8 c.c. per kilogram of methyl alcohol after the preliminary injection of 10 mg. morphin sulphate per kilogram. In a very short while, a 2 per cent. solution of sodium bicarbonate was given orally, 50 c.c. per kilogram. Emesis occurred in only one of the dogs, the other three retaining all of the solution thus administered. All four died, as shown in Table 4.

As may be seen from Table 4, treatment with the sodium bicarbonate was instituted promptly and was pursued vigorously. In three cases, all of the bicarbonate administered was retained, emesis not occurring. Unfortunately, however, plasma bicarbonate carbon dioxid determinations were not carried out on these animals, so that it cannot be stated positively that the alkali reserve was kept at a high level, as probable as this is. In order to meet this objection, three dogs were injected with the customary dose of 10 mg. morphin sulphate per kilogram and then given orally 8 c.c. of methyl alcohol per kilogram. These animals were then treated by the slow intravenous injection of 5 per cent. solution of sodium bicarbonate, from twenty to

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16. Collip and Backus: The Alkali Reserve of the Blood Plasma, Spinal Fluid and Lymph, *Am. J. Physiol.* **51**:551, 1920.

ninety minutes being consumed for the injection of the dose of 25 c.c. per kilogram. Vomiting, purging, and mild convulsions occurred, but, on the appearance of such symptoms, the injection was immediately discontinued temporarily, so that death was not caused by the injection in any instance that we could determine. Three of the four animals succumbed, one of these showing a plasma bicarbonate carbon dioxide value of 60.7 c.c. shortly before death. The results are shown in Table 5.

TABLE 4.—RESULTS OF ORAL ADMINISTRATION OF SODIUM BICARBONATE

Number of Experiment	Weight of Dog in Kg.	Dose of Alcohol in C.c. per Kg.	Lapse Before Treatment, Min.	Amount of Sodium Bicarbonate per Gm. in 24 Hours, Gm.	Length of Survival
76	17.5	8	88	4.5	24 hours
76-a	8.63	8	75	5.0	24 hours
77	5.68	8	39	5.0	96 hours
78	9.09	8	58	2.5	48 hours

In every instance, death had occurred some time prior to this; the animals were found dead at the expiration of the time given. It is interesting to note that the animal surviving longest (77) vomited frequently and profusely.

TABLE 5.—RESULTS FROM SLOW INTRAVENOUS INJECTION OF 5 PER CENT. SODIUM BICARBONATE

Number of Experiment	Weight of Dog in Kg.	Dose of Alcohol in C.c. per Kg.	Lapse Before Treatment, Min.	Amount of Sodium Bicarbonate per Gm. in 24 Hours, Gm.	Length of Survival
79	5.7	8	339	1.25	96 hours
80	9.8	8	50	1.25	Recovered
81	7.0	8	250	1.25	72 hours

From these experiments that we have carried out on dogs, it is apparent that the resistance of these animals to the poisonous action of methyl alcohol is quite variable, but that the majority will succumb to a subcutaneous or oral dose of 8 c.c. per kilogram. This is in fairly close agreement with the results previous workers have obtained, the "almost always" fatal dose being placed by them a little higher. It must be remembered that there is the possibility of a seasonal variation in the resistance; but this factor is unimportant in the present study, for all of the experiments were carried out at the same season.

While there is a reduction of the reserve alkali of the blood, as determined by the Van Slyke-Cullen method, in most of the animals examined, this is not invariably the case, and the reduction is by no means always commensurate with the severity of the symptoms. A marked reduction may occur in a dog showing only slight evidence of intoxication; while the reverse is occasionally seen, an animal suc-

cumbing to the fatal action of the alcohol and yet preserving a normal alkali reserve.

The rapid method employed by us in administering the bicarbonate is, we grant, entirely unlike the method of administration that would be employed on a human patient; nevertheless, we feel that the disastrous results obtained by it should serve as a warning against the too ready use of intravenous injections of hypertonic solutions of sodium bicarbonate.

Attractive as it is in theory, the results we have obtained by the use of alkaline therapy in the treatment of methyl alcohol poisoning<sup>17</sup> are not encouraging. It is interesting to note that Davis and Whipple<sup>18</sup> were similarly unsuccessful in the employment of sodium carbonate in the treatment of delayed chloroform poisoning.

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17. Gettler and St. George: Wood Alcohol Poisoning, *J. A. M. A.* **70**: 145 (Jan. 19) 1918.

18. Davis and Whipple: The Influence of Drugs and Chemical Agents on the Liver Necrosis of Chloroform Anesthesia, *Arch. Int. Med.* **23**:636 (June) 1919.

# THE CONSTANCY OF THE VOLUME OF THE BLOOD PLASMA \*

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## INTRODUCTION

Until about the middle of the nineteenth century no observations as to the total blood mass in the human body were presented by either clinicians or physiologists. In 1854, Welcker<sup>1</sup> attempted to determine the quantity of blood in the bodies of two criminals by means of a washing out method, and he established as normal the figure of  $\frac{1}{13}$  of the body weight, which has remained the standard commonly adopted up to the present time. Even today, after a considerable series of investigations of this problem by various workers, figures given for the total blood volume in man are approximate and not absolute. The results usually quoted vary from  $\frac{1}{10}$  to  $\frac{1}{21}$  of the body weight. This uncertainty regarding the actual amount of circulating blood is largely due to technical difficulties. Clinical methods for determining the blood volume now available, however, yield results consistent enough to furnish a figure approximating the true volume and to afford data from which relative changes in the blood mass may be determined.

It is the purpose of this paper to show that the plasma volume in man, in contradistinction to the total blood volume, tends to be a physiologic constant, except under certain stated conditions. The evidence consists of data obtained by blood volume determinations in five normal and twenty-five abnormal individuals. With reference to changes in the blood, the latter cases include examples of extreme variations in total blood volume, corpuscle content, and so forth.

## METHOD

The total mass of circulating blood may be determined by a number of indirect methods. For recent reviews of these, reference may be made to the papers of Keith, Rowntree and Geraghty<sup>2</sup> and Salvesen.<sup>3</sup>

\* From the Medical Clinic of the Massachusetts General Hospital. This is Study 6 of a series of studies of the physiology and pathology of the blood from the Harvard Medical School and allied hospitals.

1. Welcker, H.: *Prager Vrtljschr* **4**:145, 1854.

2. Keith, N. M.; Rowntree, L. G., and Geraghty, J. T.: *Arch. Int. Med.* **16**:547 (Nov.) 1915.

3. Salvesen, H.: *J. Biol. Chem.* **40**:109, 1919.

The vital red method was used for the present study. In principle it consists in the colorimetric determination of the dilution in the plasma of a known amount of a dye, vital red, which has been injected intravenously and allowed to circulate for a period of four minutes, when the sample of blood required for the determination is withdrawn. Having obtained the plasma volume in this manner, the total volume may be calculated from the proportion of corpuscles to plasma as shown by the hematocrit.

Remarkably constant results have been obtained with this method in man by Keith, Rowntree and Geraghty, the total blood mass measuring  $\frac{1}{11.4}$  of the body weight in a series of eighteen normal men.<sup>2</sup> The same method as modified and used in dogs by Dawson, Evans and Whipple,<sup>4</sup> and the acacia method of Meek and Gasser,<sup>5</sup> show close agreement with each other, and the values reported by these observers for normal dogs per kilogram of body weight approximate those found in man.

Total blood volume determinations have also been made in a variety of conditions with the carbon monoxid method, a method which in the hands of Haldane and Smith<sup>6</sup> gave values ranging from  $\frac{1}{20}$  to  $\frac{1}{16}$  of the body weight in fourteen cases examined. The value  $\frac{1}{20}$  was obtained in a patient of an extremely obese type. Later, Haldane and Douglas<sup>7</sup> made repeated observations with the carbon monoxid method on each other and found a mean value for the total blood volume from which variations did not exceed 8 per cent., in excess or deficiency, except in one instance for each subject. Salvesen<sup>8</sup> obtained an average value for normal men of  $\frac{1}{16.8}$  of the body weight, and Plesch<sup>9</sup> found  $\frac{1}{18}$  as an average value in four cases with the same method. In anemic conditions Lorrain Smith<sup>10</sup> found values in chlorosis of  $\frac{1}{9.2}$  of the body weight and  $\frac{1}{8.9}$  for pernicious anemia; volumes which represent enormous increases over the values obtained for normals by the carbon monoxid method. Finally, Douglas<sup>10</sup> secured constant results in rabbits which agreed closely with the Welcker method, approximating  $\frac{1}{21}$  of the body weight in male animals.

The difference in results between the vital red and carbon monoxid methods is not easily explained, but an important consideration concerning it will be found at the end of this paper. The variability in

4. Dawson, A. B.; Evans, H. M., and Whipple, G. H.: *Am. J. Physiol.* **51**:232, 1920.

5. Meek, W. J., and Gasser, H. S.: *Am. J. Physiol.* **47**:302, 1918.

6. Haldane, J. S., and Smith, J. L.: *J. Physiol.* **25**:331, 1900.

7. Douglas, C. G.; Haldane, J. S.; Henderson, Y., and Schneider, E. C.: *Phil. Tr. Roy. Soc., London, Series B*, **203**:195.

8. Plesch, J.: *Ztschr. f. Exper. Path. u. Therap.* **6**:380, 1909.

9. Smith, J. L.: *Proc. Physiol. Soc.*, Dec. 9, 1899, p. 6.

10. Douglas, C. G.: *J. Physiol.* **33**:493, 1906.

results with the carbon monoxid method may be more apparent than real, as Boycott<sup>11</sup> suggests, but it seems probable that the values generally accepted for the blood volume in anemia, based on Smith's figures, are too great as may be seen by results in similar cases quoted here.

There remains to be mentioned the conception of Dreyer and Ray<sup>12</sup> that the volume of the blood in mammals is directly proportional to the surface area of the body. They believe that the practice of expressing blood volume as a per cent. of body weight is erroneous and misleading, and that it should be expressed in the formula  $B. V. = \frac{B. W.}{K}$  in which K is a constant which must be worked out for each species. The formula has recently been extended to application in man and used by Bazett<sup>13</sup> in determining the amount of blood lost by operative procedures. As adopted for man the formula is  $B. V. = \frac{B. W.}{0.67}$ . This formula yields a blood volume in man equivalent to approximately  $\frac{1}{9.4}$  of the body weight, a higher figure than has been obtained by any of the other methods.

#### RESULTS IN NORMAL INDIVIDUALS

It is unfortunate that more figures concerning the blood plasma volume in normal men are not available. At present, in addition to the data presented here, the figures of Keith, Rowntree and Geraghty<sup>2</sup> alone may be referred to.

In Table I are presented the data of the five normal individuals in this series.<sup>14</sup> The total volume is  $\frac{1}{12.2}$ , or 8.7 per cent. of the body weight, as compared with 8.8 per cent. as found in the series of Keith, Rowntree and Geraghty. The average plasma volume expressed as a fraction of the body weight is  $\frac{1}{19.6}$ , or 5.1 per cent., which agrees closely with the figure of  $\frac{1}{19.4}$  in the above series. Data of this type as well as that obtained in animals by the vital red method<sup>4</sup> reveal only slight variations in the plasma volume in normal individuals per kilogram of body weight. An investigation by Bogert, Underhill and Mendel<sup>15</sup> concerning the regulation of the blood volume after injections of saline solutions leads to the same conclusion.

11. Boycott, A. F. : J. Path. & Bacteriol. **16**:485, 1911.

12. Dreyer, G. and Ray, W.: Phil. Tr. Roy. Soc., London **201**:159, 1910.

13. Bazett, M. C.: Medical Research Committee. Wound Shock and Hemorrhage, Report 5 1919.

14. It must be emphasized again that the figures presented in the tables in this paper are not put forward as absolute values. Their value lies rather in the consistency of results obtained with the vital red method, and they offer a working basis for problems concerned with blood volume. The vital red method and modifications of it are the only methods available by which the plasma volume is directly estimated.

15. Bogert, L. J.; Underhill, F. P., and Mendel, L. B.: Am. J. Physiol. **41**:189, 1916.

## RESULTS IN POLYCYTHEMIA

In three cases of polycythemia vera, as shown in Table 2, the average total volume is 13.2 per cent., or  $\frac{1}{7.3}$  of the body weight, the increase above the normal figure (approximately  $\frac{1}{12}$ ) being entirely due to the great increase in the total number of corpuscles which average 2.5 times the number found in normal men. The plasma fraction of the body weight varied from  $\frac{1}{16.2}$  to  $\frac{1}{21.2}$ , the average being  $\frac{1}{19.3}$ . Thus, while the plasma volume in polycythemia is the same as in normal individuals, the total blood per kilogram, in the cases studied, averages 47 c.c. more than in the normal. The relatively high plasma volume in Case 8 is difficult to explain. This patient had had a long course of treatment with radium and the roentgen ray.

## RESULTS IN PERNICIOUS ANEMIA

The seven cases of pernicious anemia have an average plasma volume of 4.9 per cent., or  $\frac{1}{20.5}$  of the body weight, and a total volume of 5.7 per cent., or  $\frac{1}{17.3}$  of the body weight (Table 3). The first four cases, with hemoglobin values ranging from 43 to 59, per cent., have plasma volumes averaging 5.4 per cent., or  $\frac{1}{18.5}$  of the body weight. Cases 13 and 14 have an average plasma volume of 4 per cent., or  $\frac{1}{25}$  of the body weight. It will be observed that in each of these cases the hemoglobin is below 30 per cent., which may account for the low plasma volumes. The condition seems to parallel that found after severe hemorrhage.<sup>16</sup> The last case, with a relatively high hemoglobin and high count of red corpuscles, has a plasma volume of 5.1 per cent., or  $\frac{1}{19.4}$  of the body weight. It is apparent, therefore, that but little variation occurs in the plasma volume in primary anemia. The reduction in the total volume of blood in cases with hemoglobin above 30 per cent. is due entirely to the low content of corpuscles. The average volume of corpuscles is  $\frac{1}{5}$  of that found for normals and  $\frac{1}{3}$  of the number in polycythemia. A total mass of 270 c.c. of corpuscles, as in Case 8, contrasts greatly with the usual quantity of about 2,000 c.c. found in the normal.

## RESULTS IN MISCELLANEOUS CASES

The group of miscellaneous cases includes one case (Case 22) of cardiac failure of the congestion type, with anasarca, and two cases (Cases 16 and 17) of chronic nephritis with extensive edema. The average results presented in Table 4 show, so far as the plasma is concerned, a remarkably small deviation from the normal. The average plasma value is 4.9 per cent., or  $\frac{1}{20.3}$  of the body weight.

16. Robertson, O. H., and Bock, A. V.: J. Exper. M. **29**:139, 1919.



TABLE 1.—DATA FOR FIVE NORMAL INDIVIDUALS \*

Case No.	Sex	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O <sub>2</sub> Capacity in C.c.	Per Cent. Hb. Calculated from O <sub>2</sub> Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Tril-lions
1	♂	63	57	91	3,628	1/17.3	5.7	2,140	5,768	1/10.0	9.1	1,372	128	4.8	27.6
2	♂	83	46	76	3,731	1/21.0	4.9	2,487	6,218	1/13.1	7.6	1,442	122	4.8	36.0
3	♂	55	54	83	2,660	1/18.4	5.4	1,610	4,600	1/11.0	8.3	1,061	106	4.0	18.4
4	♂	67	50	82	3,343	1/20	5.0	2,137	5,480	1/12.2	8.2	1,265	119	5.2	28.0
5	♂	69	49	77	3,380	1/20	5.0	1,901	5,281	1/13	7.7	.....	...	5.9	26.4
Average		67	51	81	3,414	1/19.0	5.1	2,053	5,467	1/12.2	8.2	...	119	4.8	26.1

\* In this and the following tables, ♂ indicates male and ♀ female.

TABLE 2.—DATA FOR THREE CASES OF POLYCYTHEMIA

Case No.	Sex	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O <sub>2</sub> Capacity in C.c.	Per Cent. Hb. Calculated from O <sub>2</sub> Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Tril-lions
0	♂	60.5	47	123	2,839	1/21.4	4.7	5,725	8,565	1/7	14.3	2,851	180	8.8	76.1
1	♂	54	47	134	2,570	1/21	4.8	4,772	7,342	1/7.8	13.7	2,934	108	10.8	75.6
8	♂	49	61	138	3,013	1/16.2	6.1	3,294	6,377	1/7.8	12.8	1,299	112	8.3	51.9
Average		54.5	51.6	129	2,824	1/19.8	5.1	4,587	7,388	1/7.3	13.7	2,304	103	9.1	67.6

TABLE 3.—DATA FOR SEVEN CASES OF PERNICIOUS ANEMIA

Case No.	Sex	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total Blood per Cent. of Body Weight	Total O <sub>2</sub> Capacity in C.c.	Per Cent. Hb. Calculated from O <sub>2</sub> Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Tril-lions
9	♂	43.0	59	70	2,567	1/17.2	5.9	408	8,055	1/14.2	7.0	284	50	1.7	5.1
10	♂	43	54	64	2,329	1/18.2	5.4	411	2,740	1/15.7	6.3	290	59	1.8	4.9
11	♂	43	48	54	2,189	1/20.5	4.9	370	2,459	1/18.2	5.4	197	43	1.2	2.9
12	♂	55	51	61	2,729	1/18.3	5.4	337	3,066	1/16.2	6.1	266	46	1.3	4.0
13	♂	55	38	44	2,136	1/20.7	3.8	264	2,400	1/23	4.3	125	28	1.1	2.7
14	♂	71	41	44	2,933	1/24.2	4.1	221	3,154	1/22.5	4.4	139	24	0.67	2.1
15	♂	59	51.5	72.5	3,040	1/19.4	5.1	1,241	4,281	1/13.7	7.8	583	78	8.2	13.9
Average		52.8	49.3	58.5	2,555	1/20.4	4.9	459	8,022	1/17.3	6.7	270	47	1.6	5.1

Consideration of the fact that the method used in determining the plasma volume and the complex nature of the problem itself leads to the conclusion that the results in these cases are quite identical with those found in the normal. It is to be noted again that the smaller total volume of 7.1 per cent., or  $\frac{1}{14}$  of the body weight, is due to the diminished volume of corpuscles associated with the anemia present in some of the cases.

#### RESULTS IN DIABETES MELLITUS

Eight cases of diabetes mellitus afford an interesting study which will be made the subject of a later report. For the purpose of this paper it is important, only, to point to the average results as shown in Table 5. The average plasma value per kilo is 48 c.c., 4.8 per cent., or  $\frac{1}{20.8}$  of the body weight. The variations of plasma volume in individual cases are greater than were found in other conditions, but the general average for the plasma volume in diabetes is close to the normal. Notwithstanding this fact, the problem of the plasma volume in diabetes, particularly during the stage of severe acidosis, remains to be worked out.

#### THE EFFECT OF EDEMA ON THE PLASMA VOLUME

It is the prevailing view in the literature that rapid alterations in body weight due to the water content of the body are associated with changes in the blood volume. With sudden increase in weight of the body the blood is said to become hydremic and with sudden losses it becomes more concentrated.<sup>17</sup> For example, Krehl<sup>18</sup> states that there is no reason why the blood should not become edematous as well as other tissues. He believes that a real hydremic plethora accompanies cardiac and renal diseases, and thinks there is no reason a priori why an increase in the total quantity of blood should not take place. Von Noorden,<sup>19</sup> on the other hand, after reviewing similar considerations, concludes that one cannot be certain of such a plethora because of the little certain knowledge of the watery content of the blood.

While it is possible that hydremia or hydremic plethora, as it is usually called, may be present in some conditions, it certainly is not found in the usual course of events, and its occurrence must be regarded as infrequent except possibly as a terminal affair. In Table 6 is presented evidence in three cases of edema to show that the relation of the blood plasma to the body weight remains undisturbed in such conditions. In Case 16, a chronic glomerulonephritis in a girl,

17. Barker, L. F.: *Monographic Medicine* 1:561, 1916.

18. Krehl, L.: *Clinical Pathology*, Ed. 2, 1907, p. 172.

19. Von Noorden, C.: *Metabolism and Practical Medicine* 2: 1907.

TABLE 4.—DATA FOR SEVEN MISHILLANOV'S CASES

Case No.	Sex	Diagnosis	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma per Body Weight	Total Blood in C.c.	Total Blood per Body Weight	Total O <sub>2</sub> Capacity in C.c.	Per Cent. Hb. Cal-culated from O <sub>2</sub> Capacity	Red Blood Cells in Mil-lions	Total Red Blood Cells in Tril-lions
16	♀	Chronic nephritis	54.5	40	47	2,200	1/24.7	387	2,587	217	45	2.0	5.7
17	♀	Chronic nephritis	40	57	76	2,291	1/17	704	3,055	290	43	3.3	10.0
18	♂	Chronic nephritis	65	47	67.5	3,117	1/20.8	1,273	4,390	758	18	4.7	20
19	♂	Myasthenia	63	46.6	78	2,953	1/21.5	2,638	4,971	1,344	123	5.3	26.6
20	♀	Gravis	60.5	56	74	3,400	1/17.8	1,075	4,473	476	57	4.4	19.0
21	♀	Secondary anemia	53.5	53.1	77	2,860	1/18.7	953	3,813	368	52	4.0	15.5
22	♂	Secondary anemia	72.2	46	81	3,333	1/21.6	2,514	5,847	1,231	111	5.0	29.7
Average		Cardiac failure	58.4	49.4	70.7	2,876	1/20.3	1,183	4,102	670	79	3.9	18.3

TABLE 5.—DATA FOR EIGHT CASES OF DIABETES

Case No.	Weight in Kilos	Plasma in C.c. per Kilo	Blood in C.c. per Kilo	Total Plasma in C.c.	Total Plasma per Body Weight	Total Blood in C.c.	Total Blood per Body Weight	Total O <sub>2</sub> Capacity in C.c.	Per Cent. Hb. Cal-culated from O <sub>2</sub> Capacity	Red Blood Cells in Mil-lions	Total Red Blood Cells in Tril-lions	Per Cent. Plasma Sugar
23	41.5	67	91	2,366	1/17.5	3,784	1/11.2	770	110	1.6	18.1	0.25
24	54.5	40	62	2,200	1/24.7	3,263	1/16.2	723	116	4.0	15.7	0.28
25	62	40	61	2,841	1/26.6	3,759	1/16.5	660	139	3.7	11.9	0.21
26	35.6	62	82.5	2,300	1/16	2,833	1/12.1	475	87	3.3	9.7	0.30
27	47	53	85	2,500	1/18.8	4,030	1/11.6	780	110	4.1	16.6	0.19
28	26	42.5	68.5	2,180	1/34	3,537	1/14.9	840	129	5.2	20.0	0.25
29	40	42.7	66.7	2,488	1/22.1	4,058	1/14.9	1,056	126	5.32	24.0	0.26
30	45	46.8	90	2,444	1/17.5	3,579	1/11.9	673	118	4.5	17.6	0.22
Average		48	75.5	2,411	1/20.8	4.8	1/13.5	812	118	1.6	17.9	

aged 16, after a loss of 13.5 kg. in weight and disappearance of all visible edema, the plasma volume per kilogram of body weight remained unchanged. No attempt is made to explain the relatively low plasma volume in this patient, who also suffered from a severe anemia. In Case 28, diabetes mellitus in a boy, aged 17, after the addition of 4 kg. in weight while on a forced fluid and increased salt intake, there was essentially no alteration in the plasma volume per kilogram of weight. In Case 22, a man, aged 75, with cardiac failure of the congestion type, and with anasarca at the time of the first observation, the figures show an apparent change in plasma volume, which, however, is only 8 per cent. and is within the margin of error. Keith, Rowntree and Geraghty<sup>2</sup> found similar results in a case of nephritis with edema.

Boycott<sup>20</sup> found that the edema which may be brought about by the administration of water to animals with uranium nephritis involved the blood as well as the rest of the tissues. The blood dilution, determined by changes in hemoglobin, in such animals was associated with fluid in the pleural and peritoneal cavities and with edema of the loose connective tissue in general. The effect on the blood volume of intravenous injection of dextrose and of sodium chlorid was found to be more prolonged in nephritic than in normal rabbits.<sup>21</sup> It is possible that in man the edema associated with acute nephritis might be reflected for a time in dilution of the blood plasma, but in sub-acute and chronic conditions the body adjustments seem to compensate for the disturbance in fluid balance, and the blood does not share in the general edema of the tissues.

A recent theory by McLean<sup>22</sup> concerning the mechanism of edema is worthy of note in the present discussion. The usual idea of edema is that the excess fluid represents an accumulation of fluid in the body, a process static in nature. McLean points out that the condition cannot be static in nature but that there must be a constant interchange of fluid and dissolved substances in edema as well as under normal conditions between the blood, tissue fluids, and contents of lymph channels in order to maintain cellular life. The condition must be regarded as an equilibrium, as Meltzer has also suggested. As the plasma volume determinations in cases of edema presented above have indicated, there is no shift of increased fluid into the blood in edema, but the balance between plasma and tissue fluids is maintained through such an interchange of fluid and dissolved substances as to maintain the fluid phase of the blood at about its normal level.

A summary of the above data is presented in Table 7.

20. Boycott, A. E.: *J. Path. & Bacteriol.* **18**:11, 1913.

21. Boycott, A. E., and Douglas, C. G.: *J. Path. & Bacteriol.* **19**:221, 1914.

22. McLean, F. C.: Personal communication.

TABLE 6.—DATA SHOWING INFLUENCE OF EDEMA ON BLOOD PLASMA

Case No.	Sex	Date	Diagnosis	Weight in Kilos	Edema per Kilos	Plasma in C.c. per Kilos	Blood in C.c. per Kilos	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Ccu. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total O <sub>2</sub> Capacity in C.c.	Per Cent. Hb. Calculated from O <sub>2</sub> Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Tril.-lions
16	♀	Jan. 9	Chronic nephritis	54.5	+	40	47	2,700	1/94.5	4.0	387	2,587	1.24	217	45.2	2.0	5.7
10	♀	Jan. 24	Chronic nephritis	46	+	41	50	1,900	1/94.5	4.1	417	2,317	1/19.8	262	60.6	2.5	5.9
16	♀	Feb. 3	Chronic nephritis	41	0	41	48	1,690	1/94.5	4.1	275	1,565	1/20.8	223	61.5	2.4	4.7
28	♂	Jan. 23	Diabetes	50	0	42.5	61.5	2,135	1/92.4	4.2	1,291	3,337	1/15	861	139.9	6.6	26.6
28	♂	Jan. 27	Diabetes	54	+	44	66.5	2,376	1/92.7	4.4	1,224	3,602	1/15	791	111.6	5.0	17.8
22	♂	Apr. 16	Cardiac failure	79.2	+	46	81	3,333	1/91.6	4.6	2,544	5,847	1/12.3	1,251	114.0	5.0	29
22	♂	Apr. 26	Cardiac failure	64.3	±	51.6	91	3,470	1/9.3	5.1	2,112	5,582	1/10.9	1,271	115.7	5.0	27.9

TABLE 7.—AVERAGE RESULTS

No. of Cases	Diagnosis	Weight in Kilos	Plasma in C.c. per Kilos	Total Plasma in C.c.	Total Plasma Fraction of Body Weight	Total Plasma per Ccu. of Body Weight	Total Cells in C.c.	Total Blood in C.c.	Total Blood Fraction of Body Weight	Total O <sub>2</sub> Capacity in C.c.	Per Cent. Hb. Calculated from O <sub>2</sub> Capacity	Red Blood Cells in Millions	Total Red Blood Cells in Tril.-lions
3	Normal.....	67	51	3,414	1/19.6	5.1	2,033	5,467	1/12.2	1,929	119	4.8	26.7
3	Polycythemia.....	54.5	51.6	2,824	1/19.3	5.1	4,987	7,388	1/7.3	2,364	163	9.1	67.6
7	Diabetes.....	52.3	49.3	2,565	1/20.4	4.9	459	3,022	1/17.3	270	47	1.6	5.1
7	Miscellaneous.....	58.4	49.4	2,876	1/20.3	4.9	1,183	4,162	1/14	817	79	3.9	18.3
8	Diabetes.....	50.4	48	2,414	1/20.8	4.8	1,368	3,721	1/13.5	817	118	4.6	17.9

## THE EFFECT OF HEMORRHAGE ON THE PLASMA VOLUME

Acute hemorrhage results in an immediate mechanical reduction of the total blood volume. If the hemorrhage is not too great, and if a reserve supply of tissue fluids is available, a flow of fluids from the tissue spaces into the circulation occurs during the process of hemorrhage so that the blood plasma may be diluted to its normal level as rapidly as possible. In a case of controlled hemorrhage four conditions may prevent a return of the plasma volume to normal: (1) lack of adequate fluid reserve in the tissues, as was found frequently

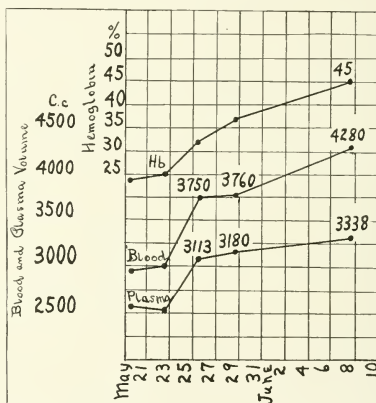


Fig. 1.—This chart is constructed from data published by Robertson and Bock, their Case 4, to show the rapid recovery of the plasma volume to normal after hemorrhage, and the gradual restoration of the total blood volume.

in soldiers wounded in action; (2) lack of adequate fluid intake by the alimentary tract; (3) a state of shock which in some degree always accompanies moderate and severe hemorrhage and in which the regulation of fluid balance between the blood and tissue fluids is disturbed; (4) a reduction in total hemoglobin below 25 per cent., as was shown by Robertson and Bock.<sup>16</sup> In the last condition, as long as the hemoglobin remains at or below 25 per cent., the plasma volume will remain below normal and no known measures can change this condition except the addition of more hemoglobin. If none of the four conditions above

named are present, the plasma tends to assume normal proportions in a comparatively short time and will then remain at the level normal for the given individual. The total blood volume, however, will remain below normal until the processes of blood regeneration have restored the normal quantity of corpuscles. Figure 1, constructed from Case 4, of Robertson and Bock, illustrates this mechanism of recovery in a case of severe hemorrhage. With a hemoglobin value of 24 per cent., the plasma remained at 2,600 c.c. Accompanying a rise in hemoglobin to 33 per cent. the plasma increased to 3,113 c.c. Two days later the hemoglobin was 38 per cent. and the plasma 3,180 c.c. Nine days later, when the hemoglobin had reached 45 per cent., the

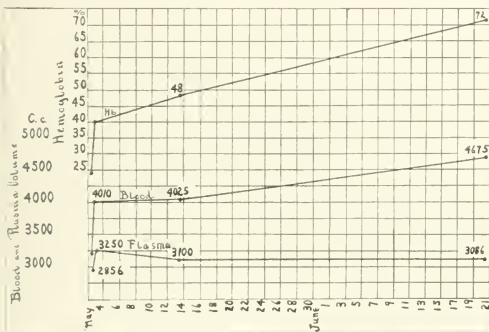


Fig. 2.—Also from Robertson and Bock, their Case 5, showing the constant level of the plasma volume as the total volume increases by the addition of red corpuscles.

plasma was 3,338 c.c. and the total volume had increased 1,300 c.c. since the original observation. Figure 2, Case 5, also from the same authors, shows a reduced plasma of 2,856 c.c. as a result of a hemorrhage which was brought up to normal by transfusion. Subsequent determinations show approximately no change in the figures. The total volume increased 650 c.c.

Figure 3 is the record of a case showing reaction following hemorrhage from a gastric ulcer. The first observation was made approximately twelve hours from the time hemorrhage apparently stopped. The plasma curve as represented shows the plasma reduction at once after hemorrhage, and after dilution to the usual level for this patient.

No further change in plasma volume occurred although the total blood volume steadily increased by reason of the addition of new red corpuscles.

Figure 4 represents the findings in another case of gastric ulcer, the observations beginning three days after hemorrhage had ceased and at a time when the plasma had already reached a normal level by dilution. The patient was transfused because of the low hemoglobin figure of 32 per cent. The plasma volume prior to transfusion was 2,685 c.c., and subsequent determinations showed very little change from this figure.

As a result of experimental hemorrhage in animals, it has frequently been reported that overdilution of the blood occurs by absorp-

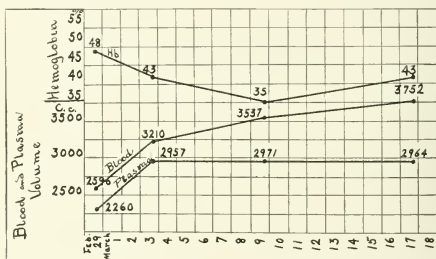


Fig. 3.—Showing the reaction of the blood following hemorrhage from a gastric ulcer, observations beginning twelve hours after the hemorrhage stopped. The plasma volume after dilution to normal, remains constant. Incidentally, this case illustrates a falling color index often seen in blood regeneration after hemorrhage.

tion of fluid from the tissues with the result that the total volume immediately subsequent to the absorption period is greater than before the hemorrhage occurred. For a discussion of this question reference may be made to the work of Boycott and Douglas.<sup>23</sup> Observation of the reaction from hemorrhage in man has failed to show that overdilution takes place and it may be said that this condition does not occur under the conditions which usually obtain. It should be understood that the blood volume determinations referred to in the work of Boycott and Douglas are "relative blood volumes" in the sense

23. Boycott, A. E., and Douglas, C. G.: *J. Path. & Bacteriol.* **13**:256, 1908.



that they are calculated from changes in the hemoglobin. Actual blood volume determinations made under the same experimental conditions employed by these authors would be interesting.

#### CHANGES IN THE PLASMA VOLUME IN CERTAIN CLINICAL CONDITIONS

While increase or reduction in the plasma volume does not occur in disease to any great degree, certain conditions are associated with concentration or loss of blood which remain to be mentioned, since they constitute exceptions to the general rule. The exceptions are

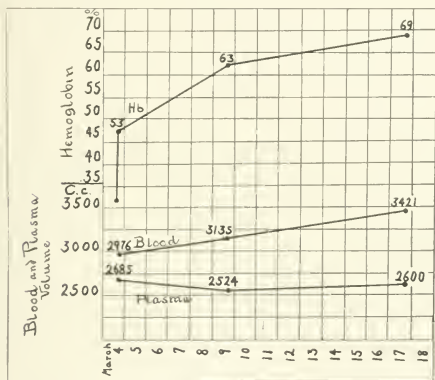


Fig. 4.—Observations begun three days after hemorrhage from gastric ulcer. Initial dilution of plasma to normal had already occurred. The effect of transfusion in this case on the plasma volume is negative, whereas the hemoglobin increased from 32 to 53 per cent.

concerned with conditions in which there is great fluid loss either directly from the circulation or through a more gradual loss of the body reserve fluid. Aside from acute hemorrhage and shock already mentioned, such conditions as acute edema of the lungs, excessive sweating, and diarrhea of severe type as seen in infants and in Asiatic cholera are outstanding examples. Cunningham<sup>24</sup> observed a patient having edema of the lungs, in whom the oxygen capacity of

24. Cunningham, T. D.: Personal communication.

the blood at the height of the attack was 25 volumes per cent. as compared to the man's normal oxygen capacity of 19 volumes per cent. Such a change in the oxygen capacity per unit volume of blood, occurring in a short time, suggests extensive contraction of the plasma volume. This finding is in agreement with experimental work on the effects of poison gas in rabbits by Haldane, Meakins and Priestley.<sup>25</sup> They found, at necropsy, extensive edema of the lungs which was believed to be associated with a corresponding depletion of the blood plasma.

Many observers have reported changes in the peripheral blood indicating concentration as a result of great sweating incident to work and exercise. No blood volume determinations are reported in such conditions except by Schneider and Havens.<sup>26</sup> These workers found the usual changes in the peripheral blood, notable increase in the percentage of hemoglobin, red corpuscle count and rise in specific gravity, which have been observed by others repeatedly. They also found, however, that abdominal massage for a brief period increased the number of red blood cells in the peripheral blood in about the same proportions as occurred after vigorous exercise. The logical deduction that they make is that a reserve store of corpuscles is present in the splanchnic area during comparative inaction which is called into the circulation by exercise. They found no alteration in the blood volume by the carbon monoxid method. Some doubt may, therefore, be entertained concerning fluctuations of the plasma volume under conditions of work and exercise.

The dehydration of the body fluids as a result of diarrhea and cholera is well known to clinicians. Marriott<sup>27</sup> has recently called attention to a condition in infants in which he described changes in the blood which simulate those found in hemorrhage and shock. The thickness of the blood in cholera requires little comment. In this condition dehydration of the tissues proceeds to an extreme state in an effort to meet the requirements of the blood plasma but concentration of the blood inevitably occurs.

The effect of altitude on the total blood volume has also been studied in both man and animals. The results in man indicate that the final alterations consist in a variable increase of red corpuscles and a slight increase in the total blood volume. Douglas, Haldane, Henderson and Schneider<sup>7</sup> report an additional increase in the blood volume after descent from Pike's Peak, and offer as an explanation

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25. Haldane, J. S.; Meakins, J. C., and Priestley, J. G.: Personal communication from J. C. Meakins.

26. Schneider, E. C., and Havens, L. C.: *Am. J. Physiol.* **36**:239, 1915.

27. Marriott, W. McK.: Paper read before Am. Soc. for Clin. Investigation, 1919.

a probable dilution of the blood plasma in order to decrease the viscosity of blood in which polycythemia had occurred as a result of residence at the summit of Pike's Peak. Such an interpretation does not coincide with present findings in cases of polycythemia vera in which the problem of viscosity is not adjusted by an increase in the plasma volume. Whatever the mechanism of adjustment may be, it is certain that such changes in volume are temporary in persons who have resumed residence at the usual altitudes.

In the present discussion may be included a condition of another type, namely obesity, in which there is known to be a reduction in the total blood volume. Haldane and Smith<sup>16</sup> report one case of extreme obesity having a volume of  $\frac{1}{30}$  of the body weight. Keith, Rowntree and Geraghty<sup>2</sup> present six cases having an average plasma volume of 37.1 c.c. per kilogram, or 3.8 per cent. of the body weight. There is no evidence that fluctuations in the plasma volume occur in this condition.

#### DISCUSSION

In relation to the present series of cases, certain additional results in the work of Keith, Rowntree and Geraghty<sup>2</sup> should be mentioned. They found an increased blood volume in the latter months of pregnancy in twelve cases. The average blood volume was 9.56 per cent. and the average plasma volume 5.7 per cent. After labor the blood volume was 9 per cent. and the plasma volume 4.9 per cent. of the body weight. Such results are in accord with volume findings in pregnancy in animals, but the increase found in women cannot be considered very great and Williams<sup>28</sup> has attached very little significance to it.

With respect to anemia, in ten cases they found three with abnormally high plasma volumes and in six the plasma values were considered slightly higher than normal. The average in eight cases was 56 c.c. per kilogram of body weight. Of three cases of pernicious anemia, two were found to have normal plasma values, 54 c.c. and 53 c.c. per kilogram, while the third had 72 c.c. It is difficult to harmonize the finding of such a high plasma volume in anemia. At variance also with the results obtained in anemia in the present series is the work of Lorrain Smith,<sup>9</sup> who found that in chlorosis and in pernicious anemia the blood volume is greatly increased. For a patient with chlorosis weighing 44.5 kg. the volume found was 6,181 c.c., or 139 c.c. per kilogram of body weight. In a case of pernicious anemia the total volume found was 6,500 c.c., or 112 c.c. per kilogram

28. Williams, J. W.: Contributions to Medical and Biological Research. Dedicated to Sir William Osler 2:1238, 1919.

In each instance the volume is comparable only to that found in polycythemia. In the case of chlorosis the total oxygen capacity was 418 c.c., which is not unlike that of Case 20 of the present series, a patient having secondary anemia of chlorotic type, whose oxygen capacity was 476 c.c. and whose total volume was 4,473 c.c., or 74 c.c. per kilogram. Likewise the case of pernicious anemia reported by Smith, with a total oxygen capacity of 195 c.c., may be compared to Case 12 of the present series, in which the total oxygen capacity was 266.4 c.c. and the total volume was 3,066 c.c., or 61 c.c. per kilogram. The results of the present investigation indicate that the blood volume is diminished in anemia in direct proportion to the decrease in corpuscles.

Of the other conditions reported by Keith, Rowntree and Geraghty, plasma values on the lower limit of normal were found as an average result in thirteen cases of chronic nephritis and hypertension, the average plasma volume being 42.8 c.c. per kilogram. In scattered cases of diabetes emaciation, myocardial insufficiency, aneurysm of the arch, chronic bronchitis, neurasthenia, and so forth, the plasma values were within the normal range.

It is important to remember that in conditions of chronic anemia, for example, no device exists for increasing the fluid volume of the blood beyond the level already attained by the patient, providing a normal tissue fluid reserve is present. Every such patient who has even a moderate fluid intake daily will have an optimum total blood plasma. Lindeman<sup>29</sup> supposed that by forcing food and fluids in cases of pernicious anemia the blood volume was thereby increased. He wrote that a patient with a large blood volume will bear a greater degree of anemia without experiencing palpitation of the heart or roaring in the ears. When the blood volume is small he thought that a less degree of anemia would produce a greater degree of exhaustion. These assumptions have not been confirmed. When symptoms are present in such cases the need is for more hemoglobin, which is the only factor that will bring relief.

Finally, a suggestion may be made concerning the relative values of blood volume methods. There is a belief that dilution of the blood as shown by changes in the hemoglobin percentage is a reliable method of studying blood volume changes. Bogert, Underhill and Mendel<sup>15</sup> recently emphasized the constancy of the hemoglobin per unit of circulating blood, and Scott<sup>30</sup> concluded that large masses of corpuscles are not held in the capillaries of any organ. The work of

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29. Lindeman, E.: *J. A. M. A.* **70**:1292 (May 4) 1918.

30. Scott, F. H.: *J. Physiol.* **50**:157, 1916.

Schneider and Havens<sup>20</sup> and of Lamson,<sup>31</sup> however, indicates that such a storage of large numbers of red cells does occur in the body and that they may readily be shifted into the peripheral circulation as, for example, by exercise or by administration of epinephrin. Clinical observation has shown that great shifts may occur in the red corpuscle count in diabetics in short periods of time. It seems, therefore, in view of the present uncertain status of our knowledge with respect to the existence of red corpuscle reservoirs, that methods for the determination of blood volume which depend on dilution of whole blood, as well as any other methods employing the red corpuscles primarily, are not theoretically sound. And when one reviews the possible variations in the total corpuscle content of the body, which in this series ranged from two trillions to seventy-five trillions, the possibility for error in such methods is obvious. On the other hand, the plasma volume is relatively a fixed constant, its fluctuations must be limited to a very narrow range and, therefore, methods by which the plasma volume can be directly determined seem to be subject to the smallest number of discrepancies and afford the most accurate results.

Theoretically, there is a mass of data, chiefly physicochemical in nature, that suggests the necessity for a stable plasma volume. The physicochemical relations existing between the blood and tissues of the body form a series of complex phenomena that is disturbed only with difficulty; the effort of the organism, as a whole, is to seek an equilibrium between plasma and cells, although, as Henderson<sup>32</sup> pointed out, equilibrium is never actually attained within the organism. It seems reasonable to suggest that the plasma volume must be free from great alterations from the normal, in quantity, if cellular activity is to proceed at an optimum rate. While absolute fixation of the plasma volume cannot occur in the nature of things, the considerations reviewed above indicate only a narrow range for the volume changes which may occur.

#### SUMMARY

Plasma and total blood volume determinations have been made by the vital red method in a series of thirty cases. The conditions represented in these patients include extremes of total corpuscle content, a very wide range in total blood volumes, and instances of edema and anasarca. It has been shown that in all of these conditions, so long as the hemoglobin is above 30 per cent., there is a constancy of plasma volume comparable to the normal. The significance of this phenom-

31. Lamson, P.: *J. Pharmacol. & Exper. Therap.* **7**:169, 1915.

32. Henderson, L. J.: *Nat. Acad. Sc.* **2**: 1916.

enon is great, since it shows that variations in the total blood volume, per kilogram of body weight, depend on the corpuscle content, except in patients with very low hemoglobin values in whom there is also a corresponding reduction of the plasma volume. Thus it happens that in a case of polycythemia with a total corpuscle content of seventy-five trillion there may be the same plasma volume per kilogram as is found in a case of pernicious anemia with a total corpuscle content of three trillion cells. In this connection attention has been called to the universally accepted high figures for blood volume in pernicious anemia and chlorosis, which vary greatly from present known and theoretical considerations.

After acute hemorrhage it has been shown that, ordinarily, rapid dilution of the plasma volume to its former normal level occurs and that it remains constant thereafter, even though the total blood volume may be much reduced by reason of loss of red corpuscles.

Certain exceptions to the general proposition of a constant plasma volume have been cited, such as hemorrhage and shock, edema of the lungs, excessive sweating and diarrhea of severe type, including cholera. Brief mention has also been made of alterations in blood volume incident to changes in altitude.

Emphasis has been placed on the necessity for a normal tissue fluid reserve. When such a reserve is present the blood plasma volume tends to remain at a normal physiologic level.

Finally, a note has been made suggesting a source of error in methods for blood volume determinations that depend on dilutions of whole blood, or primarily upon the corpuscle content. Methods by which the more fixed plasma volume may be directly determined seem to offer the most accurate results.

#### CONCLUSIONS

1. The constancy of the plasma volume in terms of body weight in health has been demonstrated by previous work and is verified in five cases of the present series. The value is  $\frac{1}{19.6}$ , or 5.1 per cent. of body weight.
2. The constancy of the plasma volume found in twenty-five cases of widely varying conditions with respect to the circulation, including edema, is a striking fact. The value for this series is  $\frac{1}{20}$ , or 5 per cent. of the body weight.
3. Variations in the total blood volume per kilogram of body weight are due for the most part to changes in the corpuscle content of the blood.

4. Previous figures quoted in the literature for the blood volume in pernicious anemia and chlorosis are too high.

5. In edema associated with cardiac and renal disease the blood plasma retains its normal value per kilogram of body weight.

6. Recovery after hemorrhage is associated with rapid restoration of plasma to the normal plasma level provided the tissue fluid reserve is adequate. Complete restoration of the total blood volume is dependent on increase in the number of corpuscles. Overdilution of the plasma after hemorrhage has not been encountered.

# HEREDITARY HEMORRHAGIC TELANGIECTASIA WITH RECURRING (FAMILIAL) HEREDITARY EPISTAXIS

WITH A REPORT OF ELEVEN CASES IN ONE FAMILY \*

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This rare affection of the skin and mucous membranes of the nose and mouth, which may involve also the cheeks, ears, tongue, lips, fingers and other parts of the body, is associated with recurring epistaxis of the familial type. In one of my cases, hemorrhage in the brain occurred, causing temporary hemiplegia and other symptoms of apoplexy. I have been able to find only thirty case reports. Steiner<sup>1</sup> found twenty-eight, including three of his own. Osler, in one of the best contributions to the subject,<sup>2</sup> reported three cases; and at that time (1901) he could find only one reference to a similar case, reported by Rendu.<sup>3</sup> Six years later, Osler<sup>4</sup> reported an additional case. However, he overlooked the cases reported by Chiari<sup>5</sup> and by J. W. Legg.<sup>6</sup> Only eight cases were found by A. Brown Kelly,<sup>7</sup> and he reported two cases of his own. None of the numerous works on dermatology, rhinology or medicine mention this condition. Hartzell<sup>8</sup> speaks of "inherited hemorrhagic telangiectasis," and also makes reference to papers by Hyde,<sup>9</sup> Crocker,<sup>10</sup> Mandelbaum,<sup>11</sup> Osler, Gjessing,<sup>12</sup> Hutchinson,<sup>13</sup> Stokes<sup>14</sup> and Majocchi<sup>15</sup> on telangiectases.

Among the most striking characteristics of this disease is the tendency to affect more than one member of a family, and the marked

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1. Steiner, W. R.: *Arch. Int. Med.* **19**:194 (Feb. 15) 1917.

2. Osler, W.: *Johns Hopkins Hosp. Bull.* **12**:333, 1901.

3. Rendu: *Gaz. d. Hôp.* **49**:1322, 1896.

4. Osler, W.: *Johns Hopkins Hosp. Bull.* **18**:401, 1907. *Id. Quart. J. Med.* **1**:53, 1907.

5. Chiari, O.: *Erfahrungen auf dem Gebiete der Hals-und-Nasenkrankheiten*, Vienna, 1887, p. 60.

6. Legg, J. W.: *Lancet* **2**:856, 1876.

7. Kelly, A. B.: *Glasgow M. J.* **65**:411, 1906.

8. Hartzell, M. B.: *Diseases of Skin*, Ed. 2, J. B. Lippincott Company, Philadelphia, 1919, p. 591.

9. Hyde, J. N.: *Brit. J. Dermat.* **20**:33, 1908.

10. Crocker: *Atlas*, pl. 71, Fig. 1.

11. Mandelbaum, W.: *Vrtljschr. f. Dermat. u. Syph.* **17**:186, 1882.

12. Gjessing, E.: *Hospitalstidende* **8**:1151, 1915.

13. Hutchison and Oliver: *Quart. J. Med.* **9**:67, 1916.

14. Stokes, J. H.: *Am. J. M. Sc.* **149**:669, 1915.

15. Majocchi, D. R.: *Acad. delle Science dell Institute di Bologna*, 1905.



tendency of a large number of the patient's relatives to suffer from epistaxis for many years. For example, two of Osler's patients were brothers and frequent attacks of epistaxis occurred in five other members of the family. Legg's patient had always shown a tendency to bleed from traumatic causes, and had painful swelling of the joints at regular intervals, resembling the "hemophilic" state. There was a history of epistaxis in three generations, and developmental telangiectases were present on the patient's face and trunk, but there was no history of hemophilia. This was the first family in which telangiectases were found. Babbington<sup>16</sup> reported a case of hereditary epistaxis in a native of Lincolnshire. The patient had been subject to frequent and violent attacks of epistaxis during all her life. She had four children, two of whom (man and woman) likewise had habitual and severe attacks of epistaxis. Recurring epistaxis had been observed for five generations. Rendu<sup>3</sup> was the first to associate the tendency to epistaxis with multiple telangiectases as manifestations of a distinct clinical entity. The condition must not be considered as being hemophilic, nor should it be confounded with the so-called hemorrhagic diathesis, nor with the acquired angiomatous lesions occurring in cirrhosis of the liver.

Hanes<sup>17</sup> described fifteen cases, including cases of his own, occurring in two families. He overlooked Jossierand's<sup>17a</sup> and Gottheil's<sup>18</sup> cases. He defines the condition as a hereditary affection, manifesting itself in localized dilatations of capillaries and venules, forming distinct groups or telangiectases, which occur especially on the skin of the face and the nasal and buccal mucous membranes, and give rise to profuse hemorrhage, either spontaneously or as the result of trauma. A hereditary tendency, both as to the formation of telangiectases and epistaxis, is the only factor constantly present. Syphilis, alcohol and other infections or intoxications do not appear to have any definite relation to this condition.

A number of cases have been reported, but with no other instances in any of the patients' families—isolated examples, in other words—of a similar condition, but not of the typical hereditary and familial variety. In some cases telangiectases, of hereditary nature, were noted in one or several members of a family, but without recurring epistaxis; in others, persistent, severe, recurring attacks of epistaxis of familial type were mentioned, but no telangiectases were reported in the patient or any of the members of the family. Such isolated

16. Babbington, B. G.: *Lancet* 2:362, 1865.

17. Hanes, F. M.: *Johns Hopkins Hosp. Bull.* 20:63, 1909.

17a. Jossierand: *Bull. Soc. méd. d. hôp. de Lyon* 1:244, 1902.

18. Gottheil, W. S.: *Internat. Dermat. Congr.* VI, 1907, Tr. 1:165, 1908.

instances have been reported by A. Brown Kelly,<sup>7</sup> Fox,<sup>19</sup> Vidal,<sup>20</sup> Lack,<sup>21</sup> Galloway,<sup>22</sup> Adamson,<sup>23</sup> Chauffard,<sup>24</sup> Babbington,<sup>16</sup> Lane,<sup>25</sup> Kopp,<sup>26</sup> Hyde,<sup>27</sup> Frick,<sup>28</sup> Létienne and Arnal,<sup>29</sup> Stokes,<sup>14</sup> Osler,<sup>3</sup> Morrow<sup>30</sup> and several others.

Hanes<sup>17</sup> believes that three factors of etiologic import are heredity, repeated traumatisms and the abuse of alcohol, and that the hereditary tendency to the disease is by far the most striking and constant feature.

Males and females are affected alike, and are equally capable of transmitting the disease to their offspring. Hemorrhage is the one constant symptom of the disease and the source of all the other symptoms. Secondary anemia may become quite serious. In the great majority of the cases hemorrhage occurs in the form of epistaxis. In some cases hemorrhage may occur from the telangiectases on the tongue, lips, fingers or buccal mucous membrane, and even rectal bleeding may occur. In my case, the patient had cerebral hemorrhage along with severe attacks of nosebleed, and on two occasions profuse bleeding occurred from the tip of the tongue and the lip.

Multiple telangiectases constitute the sole characteristic of this condition. Most commonly they occur on the buccal and nasal mucous membranes and lips. They have been noted on the face, feet, hands, ears, scalp, neck, forearms and chest. Coe,<sup>31</sup> Chauffard,<sup>24</sup> Chiari<sup>5</sup> and Legg<sup>6</sup> have mistaken these cases for hemophilia.

Pringle,<sup>32</sup> in discussing Sequeira's case,<sup>33</sup> reported a case of telangiectases of the skin associated with hemorrhage from the throat and severe hemoptysis from a large dilated blood vessel on the epiglottis. Phthisis was not present. Nearly all the hereditary cases that I was able to find recorded in the literature have been epitomized by Weber,<sup>34</sup> Hanes,<sup>27</sup> Kelly<sup>7</sup> and Steiner;<sup>1</sup> Stokes<sup>14</sup> reviewed many of the isolated instances, particularly the generalized telangiectasia cases.

19. Fox, T. C.: *Brit. J. Dermat.* **20**:145, 1908.

20. Vidal, E.: *Bull. et mem. Soc. Med. d. hôp. de Paris* **81**:186, 1880.

21. Lack, L.: *Proc. Roy. Soc. M., London* **2**:109, 1908.

22. Galloway, J.: *Proc. Roy. Soc. Med., London* **4**:42, 1910.

23. Adamson, H. G. P.: *Proc. Roy. Soc. Med., London* **1**:44, 1907.

24. Chauffard: *Bull. et mém. Soc. méd. de Hôp. de Par.* **13**:352, 1896.

25. Lane: *J. Heredity* **7**:132, 1916.

26. Kopp, K.: *Arch. f. Dermat. u. Syph.* **38**:69, 1897.

27. *Loc. cit.*, Ref. 9.

28. Frick, W.: *J. Cutan. Dis.* **30**:334, 1912.

29. Létienne, A. and Arnal, E.: *Arch. gén. de méd.*, May, 1897, p. 513.

30. Morrow, P.: *J. Cutan. and G.-U. Dis.* **12**:74, 1894.

31. Coe, J. W.: *J. A. M. A.* **47**:1090 (Oct. 6) 1906.

32. Pringle: *Proc. Roy. Soc. Med., London* **6**:129, 1912.

33. Sequeira, J. H.: *Brit. J. Dermat.* **25**:154, 1913.

34. Weber, F. P.: *Brit. J. Dermat.* **20**:159, 1908. *Proc. Roy. Soc. Med., London* **1**:44, 1907.

Weber concludes: (1) That the disease affects and is transmitted by both sexes. (2) That the hemorrhage in most cases is only from the nasal mucous membrane; in some cases also from the lesions on the tongue, fingers and cheeks. (3) That in most cases the morbid syndrome is not connected with any hemophilic tendency, or any diminution of blood coagulability. (4) That the cutaneous angiomas usually first attract attention toward middle life. (5) That in most cases a tendency to nose bleeding has been present from early life, or, at all events, many years before cutaneous angiomas were observed. (6) That with advancing years attacks of hemorrhage and the anemia become more severe. The telangiectases are disseminated more or less numerous over the face, lips and ears, and on the mucous membrane of the buccal cavity and nose.

In Osler's third case there were some lesions about the trunk and hands. In Kelly's cases the finger tips were involved, and in one the nail bed, as in Weber's case. In Chauffard's case there was no heredity, and although not truly a hemophiliac, the patient bled easily from the gums, and the least pin prick bled freely. Slight arteriosclerosis was present.

Wilson's<sup>35</sup> case of "eruptive angiomata" occurred in a man, 30 years of age. He had epistaxis and bleeding from the gums. Red "spots" were noted on the face, neck, arms and hands. In Bligh's case<sup>36</sup> bleeding occurred from the angiomas. Fearnside's<sup>37</sup> reported telangiectases in six children, associated with protracted diarrhea, wasting, edema, purpura and erythema. No other members in the families were affected.

No epistaxis was noted, and no mention is made of hemorrhages (external and free) in the patients or any of their relatives. In these cases the various rashes were the expression of vascular dilatation, particularly telangiectases. The rashes were the result of wasting, due to the protracted diarrhea. Erythema was present in all (six) cases, but purpura was present only in two cases. The patients were one boy aged 3 years, and five girls aged 10, 3, 5 and 9 years, and 17 months respectively.

Adamson's<sup>38</sup> patient was 28 years old, and had telangiectases on both sides of the neck, chest and cheeks. No hemorrhages were noted and no other member in the family was similarly affected.

Sequeira<sup>39</sup> reported the case of a woman, aged 55, who had red "spots" on the face and fingers. She had hemorrhages from one of

35. Wilson, E.: *J. Cutan. M. & Dis. Skin* **3**:198, 1869.

36. Bligh, W.: *Lancet* **1**:506, 1907.

37. Fearnside, E. G.: *Brit. J. Dermat.* **24**:35, 1912.

38. Adamson, H. G.: *Proc. Roy. Soc. M., London* **2**:128, 1908.

39. Sequeira, J. H.: *Proc. Roy. Soc. Med., London* **6**:128, 1912.

the telangiectases. One daughter had epistaxis; no other relative had a similar affection. The spots on the left index finger bled spontaneously several times in the course of three or four years. She had attacks of epistaxis nearly every morning for several years. She may have had a chronic renal condition. Hypertension and thickening of the retinal vessels were noted. She had punctate patches on the tongue, cheeks and lips.

Wilson's case<sup>23</sup> is not included in the lists of reported cases by either Steiner or Hanes. In this case copious bleeding from the gums and nose occurred, and later "red papulae with diffuse areola"—angiomas—developed suddenly on the face, neck, hands and arms. Anderson's patient was a house painter, aged 39 years. Angiomas first appeared when the patient was 11 years of age. He had rectal bleeding. Mandelbaum<sup>11</sup> described a case occurring in a man, aged 30 years. He had syphilis at 17. At 21 he developed vascular lesions on the face. Later on they appeared on the neck, limbs and chest. These lesions were disseminated purplish red nodules varying in size from a pinhead to a linseed.

Ullmann<sup>41</sup> reported the case of a woman, aged 40 years, who had roundish purplish angiomas on the face varying in size from a hempseed to a small pea. Later more lesions developed, even on the tracheal and bronchial mucous membrane. Hemoptysis occurred. The patient died from pneumonia. At the necropsy angiomas were found in the skin, respiratory mucous membrane, rectum, urethra and liver. This case is not of the hereditary type, as no mention is made as to any of the patient's relatives being similarly affected or as suffering from epistaxis.

Chauffard's patient<sup>24</sup> was a woman, aged 50 years. She had very frequent attacks of epistaxis. Many telangiectases were present on cheeks, forehead, ears, septum of nose, lower lip and tip of tongue. Secondary anemia was found. Heredity could not be established.

Vidal<sup>20</sup> recorded the case of a woman, aged 31 years, who had telangiectases on the breast, neck, wrists, forearms, thighs, feet, back of hands, back and abdomen. She sometimes had a little nosebleed. No similar condition was noted in any other member of the family.

Létienne and Arnal<sup>29</sup> reported a case occurring in a woman, aged 27 years. She developed punctiform vascular dilatations.

Shield<sup>42</sup> reported a case in which there was a portwine nevus of both hands and feet, with spots on the extremities and the face and chin.

40. Anderson, W.: *Brit. J. Dermat.* **10**:114, 1898.

41. Ullman, C.: *Arch. f. Dermat. u. Syph.* **35**: 1896.

42. Shield: *Brit. J. Dermat.* **19**: (July) 1907.

Crocker<sup>40</sup> reported a case in a girl, 7 years of age, with an enormous number of dilated vessels, beginning at 5 years of age, and occurring on the face, back of forearm and hand.

Telangiectases, symptomatic of disturbance of the general circulation are not infrequent, either when the heart itself is at fault, or when some distal portion is involved, sometimes by disease of the lungs, spleen, liver or thyroid. In exophthalmic goiter the circulation may be disturbed considerably and telangiectasis may form.

Kennan<sup>43</sup> reported two cases (a boy and a girl) of multiple telangiectases associated with recurring epistaxis, occurring in twins, aged 10 years. The telangiectases on the face of both children were first noticed four years before, following an attack of measles. The boy's nose bled frequently. Only a few "spots" were present on the mucous membranes in both cases. The father of the children bled occasionally from the nose. He has three brothers. Each one bleeds frequently from the nose, but a sister has never had epistaxis. A girl aged 14 years, has frequent epistaxis. Another girl, aged 12 years, has occasional nosebleed. In none of these cases has bleeding occurred from anywhere except the nose. There was no history of the occurrence of telangiectases in any of them, except in the two children (twins).

Lack<sup>21</sup> reported a case of telangiectases with epistaxis in a woman, 53 years old. She suffered from epistaxis for thirty years. At times bleeding was profuse, and always from the anterior part of the septum on the right side. She had typical nevoid spots on the right cheek, lips, tongue, palate and chest. The patient thought that these lesions sometimes disappear. There was no history of a tendency to bleed in other ways: no history of similar disease in other members of the family. The patient had seven children, and brothers and sisters, but all were well.

Galloway,<sup>22</sup> reported a case of multiple cutaneous telangiectases of recent origin, in a man 35 years of age. The patient had had repeated attacks of malaria. He was tuberculous. The sputum contained tubercle bacilli. Blood clotting time was normal. Red spots developed "ten months ago," mainly on the face, neck and shoulders, some on the arms and legs. They were "spider" telangiectases, "spider or stellate-angiomas." The liver was enlarged. The lesions bled profusely when traumatized. No telangiectases were seen on the mucous membrane of the buccal cavity, nasopharynx or larynx. The patient was not hemophilic. No history was obtainable of a similar condition in any other member of his family. This case resembles the hereditary type, but it is probably a case of the type appearing rapidly in certain

43. Kennan, R. H.: *Med. Press & Circ.* **33**:458, 1902.

patients with cirrhosis of the liver. Electrolysis and carbon dioxide snow was tried satisfactorily in this case.

Kopp<sup>44</sup> reported the case of a young man, aged 19 years, who eighteen months before noticed some small red angiomas over the scrotum and legs, and later on the trunk and arms. No history of a similar condition in any other member of the family was obtained.

Hutchison and Oliver<sup>45</sup> reported three cases in which frequent attacks of epistaxis had occurred since early years, with a definite history of nosebleed in other members of the family. Two of the patients showed multiple telangiectases of the face, with lesions on the buccal mucous membrane.

CASE 1.—A carman, aged 49 years, widower, had attacks of epistaxis all his life; sometimes bled from the lips, gums, ears and rectum. Red spots were present on the nose, cheeks, ears, lips, and a few on the fingers; several punctate lesions were noted on the septum of nose. There was secondary anemia, 3,250,000 erythrocytes. Blood Wassermann was negative. The lesions in the nose were cauterized without checking the epistaxis. Calcium lactate, 15 grains, three times daily, did no good. Diathermy applied to the lesions on the lip was effectual.

CASE 2.—The father of the first patient, aged 77 years, had frequent attacks of bleeding since childhood, with occasional bleeding from the rectum and gums. He had had spots on the face for years. Telangiectases were present on both ears and cheeks, and on the inside of the nose. They were numerous on the tip of the tongue. A few lesions were present on the lips. There was secondary anemia. Patient denied venereal disease.

CASE 3.—John G., aged 25 years, a son of the first patient, had epistaxis for a long time. There was no history of chilblains. He denied venereal disease. There were some miliary red spots on the tip of the tongue and the mucous membrane of the lips; a few were present on the right shoulder and there were two raised pinkish lesions on the right cheek.

Morrow<sup>30</sup> reported an unusual case of telangiectases, occurring in a girl, aged 10 years. When 5 months old she had frequent convulsions. During the course of these seizures patches of telangiectases developed on the face and body. Spots were noted on the left cheek, chin, face, nose and malar regions. She was a weakminded child. No mention is made of epistaxis, or of any similar condition in any other member of the family.

Hanes<sup>17</sup> reported recurring hemorrhages in four generations of one family. Multiple telangiectases of the skin and mucous membranes were noted on the gums, tongue, face, fingers, under the nails, and on the right lower eyelid. The patient was a woman, 53 years old. She was subject to severe nosebleed for three years. Her mother died at 48, from heart disease and dropsy, and she, too, had severe epistaxis all her life. Her mother also had red spots on the face and lips, and in the mouth. The patient's two brothers had epi-

44. Kopp, K.: Arch. f. Dermat. u. Syph. **38**: (Jan.) 1897.

staxis all their lives and both exhibited typical red spots on the face and lips.

The patient had secondary anemia of a severe type (erythrocytes, 1,500,000; hemoglobin, 15 per cent.). Her son, aged 33 years, was not subject to recurring epistaxis, but had severe hemorrhages from telangiectases on the lips and tongue, and from under the nail on the left middle finger. He occasionally bleeds from the nose. Hanes also reports the case of the other son, aged 32 years, and of a daughter, aged 18 years. He describes another family, with recurring epistaxis in sisters, and multiple telangiectases affecting chiefly the mucous membranes. No symptoms of hemophilia were present in any of these cases. The three sisters were aged 46, 26 and 28 years, respectively, and two brothers were aged 34 and 38 years, respectively. The two brothers both have nosebleeds, but neither has telangiectases. On searching the literature Hanes found thirteen other families recorded. He mentions those of Babbington,<sup>10</sup> Legg,<sup>6</sup> Chiari,<sup>5</sup> Chauffard,<sup>24</sup> Rendu,<sup>8</sup> Osler,<sup>2</sup> Osler,<sup>4</sup> Kelly,<sup>7</sup> Ballantyne,<sup>40</sup> Hawthorne,<sup>46</sup> Weber,<sup>47</sup> Phillips<sup>48</sup> and Waggett.<sup>49</sup> As treatment, he advises the destruction of the telangiectasias by the use of the chronic acid bead, followed by an alkali. Repeated cauterizations may be necessary within the nose.

Létienne and Arnal<sup>20</sup> reported the case of a woman, aged 27 years, suffering from exophthalmic goiter, who had a shower of telangiectases over the sternum, and over the remainder of the body. They disappeared on pressure. The macular lesions were round and oval in shape, scarlet to dark red in color, and of variable size. The shoulders and neck were free.

Hyde<sup>27</sup> reported four cases.

CASE 1.—A woman, aged 57 years, had symmetrically placed telangiectatic macules on the cheeks, more conspicuously displayed on the left side. The lesions varied in size from a small pinhead to half a split pea. There was one spot over the left sternoclavicular articulation. There was no history of epistaxis, or a similar condition in any other relative.

CASE 2.—A widow, aged 50 years, had a lesion on the right side of the brow, and a small lesion on the left cheek which disappeared on firm pressure. On the right cheek were dull purplish-red puncta, disappearing on pressure. There were a few scattered papules on the scalp. The urine contained renal casts and albumin. The heart was hypertrophied.

CASE 3.—A woman, aged 43 years, had one typical vascular lesion on the upper lip. A few small telangiectases were present in the upper part of the chest and there were some distended capillaries on the cheeks.

CASE 4.—A young woman, aged 24, had diffuse redness over the forehead and cheeks.

45. Ballantyne, A. J.: *J. Glasgow M. J.* **70**:256, 1908.

46. Hawthorne, C. O.: *Lancet* **1**:90, 1906.

47. Weber, F. P.: *Lancet* **2**:160, 1907.

48. Phillips, S.: *Proc. Roy. Soc. Med., London* **1**:64, 1908.

49. Waggett, E. B.: *Proc. Roy. Soc. Med., London* **1**:70, 1908.

Wise<sup>50</sup> reported a case of infective angioma of Hutchinson or angioma serpiginosum. Hutchinson, Crocker and Dore reported a case by Pringle.<sup>32</sup> Two cases were reported by Howard Fox in 1911. The patients were also examined by Wise.<sup>50</sup>

Frick<sup>28</sup> reported an unusual case of dilated capillaries in a man, 50 years of age, a landscape gardener, expressman and laborer. The skin trouble began fifteen years before on the nose, then appeared on the cheeks, neck and forehead. He never used alcoholics or tobacco. The backs of the fingers were also involved. The mucous membranes of the mouth and nose also contained dilated capillaries. No mention is made of epistaxis. Blood coagulability was normal. The patient committed suicide.

Terrell<sup>51</sup> reported a case of acquired general capillary telangiectases in a woman, 47 years old. Bright red discoloration of the skin on the back of her wrist was due to a dilatation of the capillaries. The trouble began when she was 32 years of age. It first appeared in small patches on the outer edge of the feet, then on the wrists and both forearms, extending up almost to the elbows. The extensor surfaces of the extremities were principally involved. Epistaxis was not mentioned. There was no history of similar trouble in any other member of the family. She had two children, who apparently were well.

Babbington<sup>16</sup> reported a family having recurring epistaxis. No mention is made, however, of multiple hereditary recurring telangiectases, and therefore, I hesitate to accept these as typical. The male patient (son of the woman whose case was reported by Babbington) died of the disease. The female patient (a sister of the man) had six girls, three of whom suffered from nosebleed during the earlier period of their lives. Other members of the family and their children have had habitual severe epistaxis—observed in five consecutive generations and for the last three generations in two branches.

Richardson<sup>52</sup> reported cases of familial epistaxis. A man, 53 years old, a teamster, gave no history of venereal disease. Spots were noticed on the face ten years or more ago. Numerous telangiectases were present on the face, about the mouth, nostrils and chin, and a few were seen on the septum of the nose. The trunk and lower extremities were clear. The coagulation time was normal. A secondary anemia was present: erythrocytes 3,400,000; hemoglobin, 55 per cent. The blood Wassermann was negative. Patient suffered from epistaxis. Of five children, two died in infancy. A daughter of the

50. Wise, F.: *J. Cutan. Dis.* **31**:725, 1913.

51. Terrell, W. H.: *Indiana M. J.* **15**:8, 1896.

52. Richardson, H. B.: *Am. J. M. Sc.* **154**:95, 1917.



old lady (sister of the patient) is well, except that she also was subject to bleeding from the nose, although less severe than that of the patient. A son (brother of the patient) was living and well. The mother died of an operation during childbirth.

The sister and brother of patient each had a daughter, of whom nothing is known as to epistaxis or spots. A maternal cousin had spots on the face and was subject to epistaxis. Her two sons and two daughters were subject to epistaxis. The patient's younger son, aged 25 years, traveling salesman, denied venereal disease. He had had epistaxis frequently ever since he could remember, three times a week. He had telangiectases on the cheeks, nose, ears and the tip of the tongue, and a few on his fingers. Rhinoscopy disclosed no telangiectases. He never bled freely from cuts. On the left side of the nose were two minute threadlike telangiectases of a radial arrangement. On the cheeks, there was a slight telangiectatic enlargement of the finer vessels which disappeared on pressure. Similar lesions were present. He had a minute angioma on the right upper arm.

Legg's patient was a man, aged 65 years. He had suffered from attacks of epistaxis since boyhood. One sister was subject to nosebleed. One son and one daughter suffered from nasal hemorrhages. The patient had numerous small nevi all over the face, forehead and trunk. They were not congenital and were first noticed when he was 40 years of age. The patient had joint pains and a tendency to traumatic hemorrhages. Legg thought the condition was due to congenital weakness of the vessels, which remained permanently in a stage of early formation.

Van Wagenen<sup>53</sup> reported the case of a woman, aged 32 years, a native of Russian Poland. Her mother had suffered from epistaxis since early childhood. Two brothers, aged 27 and 21 years, respectively, suffered from nosebleed since childhood but never had any hemorrhages from any other part of the body. They had spots on the tongue, nasal septum, face and arms. The patient had bleeding from the tongue and nose for some time. There was no swelling of the lower extremities. She had had no severe hemorrhages from slight wounds. Blood coagulation time was normal. The erythrocytes numbered 3,600,000; hemoglobin, 80 per cent. The Wassermann was negative. Van Wegenen used thrombokinasase to check the bleeding, and administered calcium chlorid or calcium lactate. Cauterization had been tried. Injection of hot water into the base of the lesions on the tongue was suggested by him.

Gundrum<sup>54</sup> reported four cases of the disease in the same family.

53. Van Wagenen, C. D.: *Med. Rec.* **109**:81, 1912.

54. Gundrum, F. F.: *California State J. M.* **17**:78, 1919.

CASE 1.—Lucy M. had ten telangiectases on the tongue, from 0.5 to 3.5 mm. in diameter. She had severe nosebleeds. Two telangiectases were noted on the nasal septum.

CASE 2.—The mother of the first patient, aged 44 years, had spots on her cheeks, ears, eyelids and nose. She had five telangiectases on the septum of the nose, and suffered from severe attacks of epistaxis.

CASE 3.—Brother to Lucy M., aged 47 years, had twenty spots on his face and nose. He did not have much trouble with nasal hemorrhages.

CASE 4.—Grandmother of Lucy M., was aged 65 years at the time of her death. She had thirty spots on the face and suffered from severe epistaxis. Treatment consisted of cauterization of all telangiectatic lesions with chromic acid bead, heat or other means to "destroy the tiny mass of dilated blood vessels.

Coe<sup>31</sup> reported the case of a physician, aged 53 years, as a "hemophilic" (erroneously), but the case was one of hereditary telangiectasia with familial recurring epistaxis, and is, therefore, included in this paper as an example of the clinical entity here discussed. The case is further described by Osler<sup>4</sup> and is reported as his fourth case of this condition. Coe reports four other cases of true hemophilia.

Osler's first case<sup>2</sup> occurred in a seaman, aged 57 years. The mother never had epistaxis. A sister died at 59, of Bright's disease. She had had epistaxis since childhood. Another sister bled from the nose and mouth. The patient reported, had one child, aged 13 years, who bled from the nose. A grand niece, granddaughter of the patient's eldest sister, also had epistaxis. The patient had syphilis when 27 years old. He had secondary anemia; erythrocytes, 2,980,000; hemoglobin from 15 to 20 per cent. Coagulation time was from five to seven minutes (Wright's). A number of telangiectases were noted on the tip and edge of the tongue.

The patient's brother, Wm. B., aged 55 years—had "spider" angiomas on the nasal septum, lips and side of the nose, on the cheeks and on the ears. He had erythrocytes, 4,488,000; hemoglobin, 71 per cent. Coagulation time was four minutes. He took calcium chlorid, 15 grains, three times daily. The second patient had cancer of the stomach, liver, lungs and brain. Seven members of his family have been subject to epistaxis.

Osler's third case is not altogether typical of the disease under discussion, because it seems to be an isolated instance not of the true family type, but of the kind that is associated with cancer of the liver and other organic disease, such as syphilis, nephritis, gall-bladder trouble, scleroderma, cardiorenal disease, etc. Osler's third case occurred in a man, aged 49 years, who had had epistaxis since childhood. There were no bleeders in the family, and none had serious attacks of epistaxis. He denied syphilis. He had a secondary anemia; erythrocytes, 3,460,000; hemoglobin, 38 per cent.

Telangiectases were present on the face, lips, tongue and scalp. His attacks of epistaxis began at the age of 10. He bled also from the telangiectatic lesions in the gums and lips.

Osler's fourth case<sup>4</sup> occurred in a physician, aged 53. He had numerous telangiectases of the skin of his face, ears and lips, and secondary anemia. He had been a nosebleeder for many years. He also bled from the "spots." The bleeding began at his tenth year. His grandfather, father and one sister had had "spots" and had bled in the same way. His son had epistaxis but no "spots." The patient did not have joint trouble. There was no severe bleeding from the cuts.

Scattering angiomas (telangiectases) of the skin are frequently found in apparently normal persons and have no pathologic significance. However, they may develop in large numbers in varying sizes on the skin of persons with diseases of the pancreas and liver, cancer, chronic jaundice from gallstones, or simple catarrhal jaundice, also in tertiary syphilis and as a result of exposure of the skin to the roentgen ray. In Osler's second case telangiectatic lesions were present in the mucous membrane of the stomach. The patient died from general carcinomatosis.

Rendu<sup>5</sup> reported a case in a man, aged 52, who suffered from repeated attacks of epistaxis. He had small superficial angiomas of the skin of the face, neck and thorax, and in the mucous membrane of the mouth. The patient's mother and brother had repeated attacks of epistaxis. His father died of dysentery, with repeated crises of melena, at the age of 55. He had a few scattered lesions over the neck and chest. Rendu used for the epistaxis, antipyrin, 50 gm.; tannin, 1 gm. and sugar 10 gm. As stated, Rendu was the first to describe this condition as a distinct clinical entity.

Fox<sup>18</sup> reported the case of a young woman, Emily B., who had epistaxis at 10 years of age; at 14 "spots" appeared in the left lower axillary region and left side of the back; later they appeared also in the right lower axillary region and lower part of the chest, becoming bilateral. She had marked epistaxis, and recently began to have bleeding from the rectum. Sigmoidoscopy showed that the lower bowel was normal. A family history of bleeding of epistaxis could not be obtained.

Kelly's<sup>7</sup> patient, aged 41 years, had suffered from severe recurring epistaxis. Her father died at 62 from the effects of frequent nasal hemorrhages. Her sister bled from the lips, mouth and nose and had multiple telangiectases on the face and hands and on the mucous membranes of the nose and mouth. There were few lesions on the scalp. The patient's daughter bleeds from the nose and has

red spots on the face. The patient died from a severe and persistent attack of epistaxis (syncope). In this case, there was a history of severe recurring epistaxis with multiple telangiectases of the skin and mucous membranes in the family for three generations.

Morrow,<sup>30</sup> Lanceplaine,<sup>55</sup> Hyde,<sup>27</sup> Kopp,<sup>44</sup> Tantarri,<sup>56</sup> Terrell,<sup>51</sup> Levi and Le Noble,<sup>57</sup> Brocq,<sup>69</sup> Mosny and Malloizel,<sup>58</sup> Gaucher and Crouzon,<sup>59</sup> Létienne and Arnal<sup>29</sup> have reported cases of telangiectasia of the more or less generalized type which were so carefully and thoroughly studied by Stokes.<sup>14</sup> Stokes says, that out of thirty-three cases which he found in his search, he noted that syphilis, plumbism, hyperthyroidism or nephritis was present in twenty-two and possibly in twenty-three.

In Gastou's<sup>60</sup> two cases syphilis was a factor. The father developed telangiectases; the daughter developed localized telangiectasia in early life. There is probably a preponderance of females over males in connection with the development of generalized and localized telangiectasia.

Mandelbaum's case<sup>11</sup> was an old syphilitic with macular, arborescent and nodular telangiectatic and angiomatic lesions, generalized over a considerable portion of the body.

Ehrmann's case<sup>61</sup> occurred in a patient with general arteriosclerosis. He had telangiectases over the trunk and on the extremities. This may have been a case of syphilis.

Stokes<sup>14</sup> reported a case in a widow, aged 34. There was no history of familial epistaxis, hemophilia or telangiectasia in any other member of the family. At 9 years of age she began to suffer from nose-bleed. The hemorrhages were severe. This recurring epistaxis ceased abruptly with her first menstruation at 12, and did not recur. Skin trouble began at 29 years. She had had a small telangiectatic lesion below the right eye for many years, and several small pink spots on the dorsum of the feet. Then the wrists, arms, legs, and, lastly, the trunk became involved. There were no lesions on the palms of the hands nor on the face at any time. The scalp, neck and shoulders were free. The configuration of the dilated venules was arborescent, stellate, or lacelike on the legs—arborescent telangiectatic figures. The mucous membranes were negative. The urine was negative. Blood coagulation time was normal. The blood Wassermann was negative

55. Lanceplaine, R.: Thèse de Par., 1904.

56. Tantarri, V.: Ann. de dermat. et syph., 1880, p. 338.

57. Levi and Le Noble: Presse méd., 1896, p. 310.

58. Mosny and Malloizel: Bull. soc. méd. d. hôp. de Par., 1905, p. 847.

59. Gaucher and Crouzon: Ann. de dermat. et syph., 1902, p. 52.

60. Gastou, P.: Bull. Soc. de Dermat., 5:71, 1894.

61. Ehrmann, S.: Wien. klin. med. Wchnschr., 57:778, 1907.

once and positive once. The erythrocytes numbered 5,580,000. He reports the case, with a review of other recorded cases, under the title "Generalized Telangiectasia in Association with Syphilis, with Peripheral Vascular Sclerosis."

Head<sup>62</sup> reported two cases of multiple hemangiomas of the skin associated with dyspituitarism.

CASE 1.—A Swedish farmer, single, aged 28 years, gave no history of venereal disease. He had been sick since 8 years of age. The telangiectases appeared when he was 14 on the penis and scrotum, later on the thighs, arms, back and abdomen. No lesions were seen on the mucous membrane of the lips, mouth or nose. There were some telangiectases on the face and neck varying in size from pin-point to 2 mm. in diameter. The Wassermann test was negative; no glycosuria; no epistaxis; pains in the toes and fingers and dull aches in the knees. Four brothers and three sisters are well. Mother died of apoplexy.

CASE 2.—A man, aged 60 years, laborer, with no history of venereal disease or nosebleed, had hemangiomas of the skin of the scrotum and the mucous membrane of the cheeks and lips. He was acromegalic and had mitral endocarditis. Family history was negative. Father and brother died of tuberculosis. The Wassermann test was negative.

Trawinski<sup>63</sup> suggested the name perivasculitis syphilitica telangiectatica for his case. His patient was a syphilitic, and showed macular, arborescent, and striate telangiectases, with gummatous infiltrates in the skin. Frick's patient<sup>28</sup> showed generalized telangiectasia, with carcinoma of the liver with metastases. Wise's case<sup>50</sup> was one of angioma serpiginosum and was studied by Pollitzer. Fox's case<sup>19</sup> showed grouped papular lesions on the trunk, associated with epistaxis in childhood and rectal hemorrhages.

Some of these cases may present features resembling Majocchi's purpura annularis telangiectodes. Majocchi<sup>14</sup> believes that there is some direct action of some toxin on the vessels which excites endothelial reaction and proliferation and brings about this condition. Cardiovascular degenerative conditions (syphilis being the most important) appear to have some etiologic relationship in a few of the reported cases of telangiectasia. Lead, alcohol, hyperthyroidism, dyspituitarism, many of the infectious diseases particularly syphilis, may have some etiological relationship in some cases. This phase of the subject needs further study and investigation.

In Chiari's two cases<sup>5</sup> (two sisters) a history of epistaxis in four generations was obtained, with multiple telangiectases on the skin and mucous membranes, and the condition was erroneously diagnosed as hemophilia. The grandmother and two brothers of the girls suffered from childhood with frequent and severe attacks of epistaxis.

62. Head, G. D.: Arch. Int. Med. **20**:24 (July) 1917.

63. Trawinski, H.: Monatsh. f. prakt. Dermat. **1**:45, 1910.

Kelly's two patients<sup>7</sup> were also sisters. Their mother, two brothers and one sister all suffered from severe nasal hemorrhages. Apparently the sister recovered from these attacks and only bled a little from the nose at the time of the menstrual periods. The two patients reported by Chiari bled from the nose since childhood and one of them also bled from the gums. Both sisters had telangiectases on the face and trunk and on the mucous membranes of the nose, tongue and lips. Their children also suffered from nosebleeding.

The other family reported by Chiari gave a history of severe epistaxis in three generations. Three members of the family suffered with severe attacks of nosebleed from childhood. They had multiple telangiectases on the skin and mucous membranes. When first seen by Chiari, one of them, a young woman aged 30, exhibited telangiectases on the skin and mucous membranes of the nose, tongue and lips. Her father and paternal aunt had the same trouble. Her sister and all her sister's children were similarly affected, and one of the children died from a severe nasal hemorrhage.

Josserand's<sup>17</sup> patient was a woman, aged 56 years, who had suffered from epistaxis since childhood. Lately she also bled from the lips, gums and tongue. She exhibited telangiectatic lesions on her neck, chest, back and arms, but in greater numbers on the face, lips, tongue and palate. One brother had nosebleed and telangiectases; another brother and her father had been subject to frequent attacks of epistaxis.

Hawthorne's patient<sup>46</sup> was 49 years of age. She had had nosebleed since childhood. There was a history of epistaxis with telangiectases in three generations. The patient's father and sister, and her nine children had frequent attacks of epistaxis. She had telangiectases on her fingers and face. Her father and sister had telangiectases on the face.

Weber's<sup>47</sup> patient was a woman, aged 60, who first noticed telangiectases on her face when she was 42. She had nosebleed and "spots" on her face, ears, lips, tongue, conjunctiva of all the eyelids, the mouth and nose. She also had some lesions on the fingers and under the nails. A daughter, aged 10 years, had frequent nosebleed but no "spots." This family gave a history of recurring epistaxis in four generations. The patient's mother had nosebleed and several "spots" only on the face. The patient had small angiomas on the posterior wall of the pharynx, in the nostrils and on the anterior surface of the epiglottis. Calcium lactate did not stop the epistaxis. Epinephrin was applied locally, and iron and arsenic were given internally.

Phillips'<sup>48</sup> patient was a married woman, aged 56, who had had nosebleed and hemorrhages from the mouth since childhood. Her

father suffered from violent epistaxis and hemorrhages from the tongue. Her sister died from hemorrhages of the gums. The patient had one daughter who had vascular lesions on the tongue and suffered from epistaxis. There was a small red patch on the tip of the tongue, which bled at times. The patient had telangiectases on the mucous membrane of the tongue, nose and mouth.

Waggett's patient,<sup>49</sup> 53 years of age, had hemorrhages from the nose for thirty-three years. He also bled from telangiectases on his face and lips. Telangiectases were also present on the mucous membranes of the tongue and nose. A sister was similarly affected.

Hulke<sup>64</sup> described a case of general telangiectases affecting chiefly the left half of the body. The condition began with the presence of a few nevoid spots in early infancy. Epistaxis is not mentioned, nor was heredity a factor.

Harris<sup>65</sup> reported a case of severe epistaxis, but the patient was suffering from hemophilia. Bligh's case of bleeding telangiectases<sup>36</sup> occurred in a man, aged 32 years, who had nevoid growths and hemorrhages, but gave no familial history. Smith<sup>66</sup> had a patient, a woman, 50 years of age, with multiple venous angiomas on the face and upper part of the trunk.

Ballantyne<sup>45</sup> reported three cases of multiple telangiectases in one family (Hollanders; Zaandam). Red "spots" were present on the palpebral conjunctiva in two and on the lips and other portions of the skin and on the mucous membranes. Several of the patients were subject to nosebleed. The man was 63, his wife 56; a healthy son, 30. A daughter, aged 26, had red spots on the face and one finger. Five of the six members of the family who were examined had telangiectases. One of the boys had spots on the inner surface of the lower lip and tip of the nose and end of his tongue. One boy had no spots, but bled from the nose.

Audry's case was a patient aged 70 years, who had nosebleed for many years. He presented numerous telangiectases on the face, tongue, palate, arms and body. His mother, a great uncle, a great aunt, two sons, five brothers and sisters were all similarly affected. His mother bled from the nose and exhibited telangiectases.

Langmead<sup>67</sup> reported a case of hereditary multiple telangiectases in a man, aged 68 years. There were thirty small vascular red or purplish nevoid lesions on the face. Some had the "spider" form. The lower lip and under surface of the tip of the tongue were involved.

64. Hulke: Roy. Med. Chir. Soc., Dec. 12, 1876.

65. Harris, T. J.: Laryngoscope **28**:890, 1918.

66. Smith, F. J.: Tr. M. Soc. London **21**:358, 1898.

67. Langmead: Proc. Roy. Soc. Med., London **3**:109, 1909.

No telangiectases were seen in the nose. For twenty years the patient bled from the nose. He was first seen by Langmead in June, 1909. He had a secondary anemia. The erythrocytes numbered 2,200,000; hemoglobin, 30 per cent. Four brothers and one sister were subject to epistaxis and exhibited telangiectases. The patient's father was similarly affected. His mother suffered from severe epistaxis only. The patient had two sons, one of whom, aged 35 years, had nevoid patches and epistaxis; the other younger son only bled from the nose. A daughter of one of his brothers had similar patches and was subject to recurring epistaxis. Telangiectases were present in eight members of this family for three generations, and nasal hemorrhage was a symptom in eleven members of the family.

Gottheil's patient<sup>18</sup> was a man, aged 40 years, who bled from his nose, tongue and lips as long as he could remember. His mother had spots on her lips and died, probably as a result of hemorrhages. Two of the patient's children, one sister and three brothers had nosebleed.

Laffont's patient<sup>68</sup> was a woman, aged 48 years, who noticed at the age of 39 or 40 that telangiectases were appearing on the scalp, face, ear, breast and back. Some had disappeared spontaneously. Since puberty she had repeated attacks of nosebleed. Her mother, at 62, had spots on her ears, neck, chest and arm; no mention is made of epistaxis. Her sister had telangiectases on her ears, back of the neck and arm, but no epistaxis. Other members of the family were similarly affected.

Gjessing<sup>12</sup> gives the history of a family in which epistaxis and telangiectases were observed for four generations; one member of the family had endocarditis and hemorrhagic retinitis. The patient whose case is reported, was a man, aged 51 years, who had had severe epistaxis since childhood. When about 25 or 30, he noticed telangiectases on his face and the mucous membrane of his mouth. Next they appeared on the ears, under the chin, on the neck, nose, tongue, hard palate and the right lower eyelid, a few spots developing on several fingers and the left arm. He has bled from the nose and the spots on the cheeks, eyelid and tongue. Two children have bled from the nose. The hemoglobin percentage was 25. Several other members in the family were similarly affected.

Hanes<sup>17</sup> and Steiner's<sup>1</sup> cases are described so well that I will not repeat the reports in detail. Hanes reported two families with recurring hemorrhages in four generations of one family, and multiple telangiectases of the skin and mucous membranes, but no symptoms of hemophilia. One woman, aged 53, had bled since childhood. Telangi-

68. Laffont: *Presse méd.* 17:763, 1909.



ectatic spots were present on the face, lips, tongue, ears, hard palate, gums and the nasal mucous membrane. In the other family four sisters had epistaxis and multiple telangiectases, affecting chiefly the mucous membranes, but no symptoms of hemophilia. A second patient, aged 46, suffered from severe nosebleed throughout childhood. She had telangiectases under the eyes, on the conjunctivae, on the lips, tongue, hard and soft palate and nasal mucous membrane.

Steiner reported three families with this condition.

CASE 1.—Family F. G. Recurring hemorrhages occurred in five generations and twenty-one members of this family; telangiectases were observed in five. The patient was a well developed man, 42 years of age, who was admitted to the hospital because of weakness, shortness of breath and frequent nosebleed. He began to suffer from epistaxis at 14. At 16, he had small hemorrhages from a red spot on the face. He denied venereal disease. Angiomas were seen on both cheeks, varying in size from pin-point to 3 or 4 mm. in diameter. Several were present on the nose, tongue, lower lip and ear. There were a few angiomas on the septum of the nose and on the left inferior turbinate. Hemoglobin percentage was 60; erythrocytes numbered 4,696,000; leukocytes 4,800. The patient was given iron and arsenic. The spots in the nose were cauterized on two occasions. The Wassermann and luetin tests were negative. The patient's father, grandfather and one aunt, all of whom are now dead, several of his children and grandchildren were similarly affected.

CASE 3.—Mrs. A. T., aged 33, bled from the nose, tongue, pharynx and hard palate. These hemorrhages seemed to have been controlled by ergot given internally and locally by tincture of ferric chlorid.

CASE 4.—Mrs. D. E., aged 25 years, bled from the nose for nine years, and then began to bleed from the tongue. Both these women (Cases 3 and 4), members of the same family, had angiomatous lesions on the face, tongue, etc.

CASE 5.—Family E. M. Recurring epistaxis occurred in three members of the family for two generations; telangiectases with recurring nasal hemorrhages were present in only one member of the family. This woman was 41 years of age. She began to have epistaxis when 25 years of age. Her gums bled easily. Eight or nine years ago she began to have red spots on her cheeks, then on the hands and wrists. She was very anemic. Erythrocytes, 2,560,000; hemoglobin, 55 per cent. (Dare); coagulation time, 4½ minutes. One sister was subject to nosebleed all her life. Another sister had a son who bled from the nose. No mention is made as to the presence of telangiectasia in any other member of the family.

CASE 6.—Family C. L. Man, aged 62 years, bled from the nose occasionally since childhood. He was a well nourished Italian. The Wassermann test was negative. Telangiectases were noted on the forehead, cheeks and nose; pinpoint, nodular and spider forms. There was a history of epistaxis and telangiectases in this family for three generations. The patient's father died at 92; he too had telangiectases and nasal hemorrhages. Of the patient's six children, only a daughter suffers from occasional attacks of nosebleed.

#### REPORT OF AUTHOR'S CASES

CASE 1.—Mrs. R. W., aged 42 years, white, married, has had severe persistent and recurring attacks of epistaxis since childhood. She has two daughters and two sons. One daughter, aged 20 years, has bled from early childhood. The other daughter, aged 11 years, has bled from the nose nearly all her life. The patient has telangiectatic lesions on the nose, nasal septum,

lips, tongue, chin and cheek. There are a few lesions on the left side of the neck, and one on the middle finger of the left hand. None are seen on the thighs and legs. The larger spots on the tip of the tongue have bled on several occasions. Bleeding from lower lip occurred on one occasion. Sometimes the hemorrhages from the nose are very profuse and uncontrollable. The patient received ferrous carbonate, sodium arsenate, calcium lactate and calcium chlorid at various times. She also used thyroid and lutein for a brief period. Secondary anemia is present. Her eldest daughter has a few spots on the tongue and one over the right clavicle and some on the forearms. The younger daughter has none on the face or body, and only two very small ones are seen on the tongue. The patient's mother, who is dead, also had recurring attacks of epistaxis and red spots. Three sisters are married. Two sisters have nosebleed; one sister, 34 years of age, bleeds profusely from the nose.

Her four children, J. H., 13; A. H., 11; M. H., 6, and I. H., 3; all suffer from epistaxis. Another sister, A. L., aged 32, bleeds from the nose. Her son, M. L., aged 8, does not bleed. A third sister, Mrs. M. C., aged 30, and two children, J. C., aged 10 and E. C., aged 5, apparently do not bleed.

Mrs. R. W. (the oldest daughter), had a "stroke" and hemiplegia Jan. 20, 1918, after a little giddy spell. This attack was due to defects in the small vessels, like those occurring in other parts of the body, or a peripheral sclerosis. Blood Wassermann tests were negative on several occasions. Blood chemical tests showed urea nitrogen 18 mg. in 100 c.c. of blood; nonprotein nitrogen, 35 mg.; creatinin, 2.20 mg.

*Urine.*—Jan. 26, 1918: Trace of albumin; sugar less than 0.1 per cent.; chlorids, 0.5 per cent.; specific gravity, 1.005; granular and hyalin casts; flat and round and caudate epithelial cells; urea, 1 per cent.; acid.

March 11, 1919: Albumin present; urea, 0.5 per cent.; amorphous urates present; total solids, 16.3 gm.; faintly acid; specific gravity, 1.009; no casts; no sugar.

July 24: Acid; specific gravity, 1.015; no acetone; no diacetic acid; slight excess of indican fifteen times normal; urea, 0.6 per cent.; no diazo reaction; slight excess of urochrome; no casts and no cylindroids; many red blood cells; many renal epithelial cells; large number of leukocytes (pus). Thirty-five ounces of urine were voided in twelve hours.

Eyes: April 30, 1919. Posterior polar cataracts in both eyes.

Blood: Coagulation and bleeding time normal. Feb. 15, 1918. Erythrocytes, 3,980,000; leukocytes, 12,600; hemoglobin, 61 per cent. Differential count: polymorphonuclears, 64 per cent.; small mononuclears, 26 per cent.; large mononuclears, 4 per cent.; transitionals, 2 per cent.; eosinophils, 3 per cent.; mast cells, 1 per cent. July 24, 1919. Erythrocytes, 300,000; leukocytes, 14,600; hemoglobin, 68 per cent.; polymorphonuclears, 60 per cent.; large mononuclears, 12 per cent.; small mononuclears, 24 per cent.; transitionals, 2 per cent.; eosinophils, 2 per cent.

The phenolsulphonethylthalein renal function test was practically normal. The blood pressure varied during the past three years between 128 systolic, and 90 diastolic, and 110 systolic and 80 diastolic.

*Comment.*—At the time she had the stroke it was difficult to decide as to the cause. One could not easily differentiate between embolism, thrombosis and hemorrhage. There was no evident source of an embolus. A faint murmur could be heard over the heart, and at times it was faintly audible at the apex, but it could be attributed to the anemia. Shortly after the cerebral hemorrhage, the systolic blood pressure was 140; however, at no time during the past three years has it been higher than the normal average, often below. She complains of a heavy feeling and numbness in the limbs, and "heaviness with giddy or dizzy feeling in the head." She has crying spells occasionally, worrying over her condition. She was seen by Dr. O. H. Perry Pepper at my request, who reported also that her clotting and bleeding time was normal.

There is no history of hemophilia in the family and none in the family bleed excessively from cuts. One son, A. W., aged 12 years, has several small telangiectases, and a large pale reddish nevus on the back of the left shoulder and one telangiectatic lesion below the right lower eyelid. He does not bleed from the nose; the eldest son, L. W., aged 23 years, apparently has neither epistaxis nor many telangiectases. There are a few over the scapular regions (supraspinous), and one lesion about four inches below and to the left of the left nipple.

At the time of the "stroke," and since, the patient, Mrs. R. W., has been seen by A. E. Roussel, F. X. Dercum, Charles Potts, W. G. Spiller, A. Gordon of Philadelphia, T. D. Taggart of Atlantic City, N. J., S. S. Butler of Camden, N. J., and others, during the past three years; however, none of them made the diagnosis of hereditary telangiectasia with recurring hemorrhages, and did not associate the nosebleed and the cerebral complications with the hereditary weakness of the vascular system. Dr. O. H. P. Pepper agreed with me in my diagnosis.

CASE 2.—Mrs. Anna L., aged 32 years; married seven years, had one miscarriage at six months, and one premature birth at eight months, the child living only twenty-four hours. Her husband had a positive Wassermann test. The patient had a positive Wassermann nine years ago. She has one boy, M. L., aged 7 years, living and well. The boy does not bleed from the nose. The patient has had nosebleed since early childhood, very frequent; bleeding stops of itself. Had influenza and pneumonia and measles. She bleeds very profusely from the left nostril. Her hands are cold, and she gets short of breath on exertion. Occasionally, she bleeds from hemorrhoids. She has seven or eight small spots over the back, on the shoulders, two small spots back of ears, several on the left side (anteriorly) of septum of nose and one or two on right side of septum. There are a few radiating dilated capillaries around the alae of the nose. She also has clubbed fingers; these are cyanosed and cold; the lips are cyanosed and get "blue" very often. Blood pressure: systolic, 95; diastolic, 70. No cardiac murmurs were heard at time of the examination, but the heart sounds were not of good quality; they were weak and muffled. She is a sister to the above patient of Case 1, Mrs. R. W., and to Mrs. E. H. (Case 3). Numerous Wassermann tests have been negative, following specific treatment taken up to a few years ago.

CASE 3.—Mrs. Eliz. H., aged 35 years, has four children. She had one miscarriage. One infant, aged 1 month, died of whooping cough. She was operated on four years ago for ruptured gastric ulcer with intestinal obstruction. She has been bleeding from the nose almost daily since childhood. She says her mother bled "terribly" from the nose for a great many years, and she thinks her death was due to these severe nasal hemorrhages. She has a pinpoint lesion above the right eyebrow, three or four spots on the right cheek over the malar bone, one pinpoint lesion on the left cheek, one inch to the left of the outer angle of the left eye; three or four lesions on right half of the lower lip; one spot on the under surface of the upper lip; one on upper gum; one spot on neck at base (right side). She gets attacks of nosebleeding even during her sleep.

CASE 4.—Marvin H., aged 5 years, was always well, except for severe nasal hemorrhages. He has had nosebleed daily, and during sleep, since 2 years of age. He has one spot on left cheek, one inch below outer angle of left eye, and one on right cheek, one inch below and in front of right ear. Several dilated capillaries are noted on right side of septum of nose. He had measles. Mother says boy "bleeds in streams from the nose" daily, which stops itself, after bleeding for five or six minutes. In these cases epistaxis was the first manifestation of the disease. While the hemorrhages have been severe and prolonged, there is only a comparatively mild secondary anemia. In appearance the patients do not look very anemic at all. Sometimes washing the

face, or using a handkerchief, or other very slight trauma is sufficient to bring on an attack of epistaxis.

*Blood Examination.*—Oct. 11, 1920: Hemoglobin, 70 per cent.; erythrocytes, 2,900,000; leukocytes, 8,000. Differential count: Polymorphonuclears, 51 per cent.; small lymphocytes, 45 per cent.; large mononuclears, 3 per cent.; eosinophils, 1 per cent. Marked poikilocytosis and anisocytosis. Blood Wassermann negative.

CASES 5 AND 6.—Aaron H., aged 11 years, and Jeanette H., aged 13 years, bleed very profusely from the nose since 2 years of age. They are the children of E. H. They have "spots."

*Blood Examination.*—Oct. 11, 1920. Jeanette H.: Hemoglobin, 75 per cent.; erythrocytes, 3,350,000; leukocytes, 7,400. Differential count: Polymorphonuclears, 72 per cent.; small mononuclears, 25 per cent.; large mononuclears, 2 per cent.; eosinophils, 1 per cent. Some anisocytosis and poikilocytosis. Blood Wassermann negative.

Aaron H.: Hemoglobin, 80 per cent.; erythrocytes, 3,250,000; leukocytes, 11,000. Differential count: Polymorphonuclears, 61 per cent.; small mononuclears, 36 per cent.; large mononuclears, 2 per cent.; eosinophils, 1 per cent. Some poikilocytosis and anisocytosis. Blood Wassermann negative.

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	Boggs	Test Tube
Marvin H. ....	5 min.	6 min.
Jeanette H. ....	6 min.	7 min.
Aaron H. ....	5 min.	4 min.

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The hereditary type of telangiectases with epistaxis is principally of three forms: (1) pinpoint, (2) spider form, the most common, and (3) nodular.

Strictly speaking, telangiectasis is a dilatation of the terminal vessels, i. e., capillaries—but it is a term used also to describe dilated venules.

Osler speaks of a type of lesion occurring often on the cheeks, nose and ears in persons exposed to the weather, and in heavy drinkers. Often there occur arborescent, distended venules on the skin of the thorax along the line of the attachment of the diaphragm. Or the lesion may occur as small pinkish spots from 2 to 5 mm. in diameter, perfectly smooth and uniform, without visible venules, which disappear completely on pressure. They may be only pinpoint in size, and are often of a vivid pink color. They may appear suddenly and last for several years and then disappear. Then, again there are small nodular forms, raised, bright purple or crimson in color, from 1 to 5 mm. in diameter. They may be congenital. They are supposed to occur sometimes with cancer of the abdominal organs especially of the stomach, but they are common in old persons and in many different conditions. The spider form is made up of a central dot, from which radiate five or six venules, or rather toward which some vessels

converge (nevus araneus). Spider nevus is often associated with cirrhosis of the liver. The spots are from 2 to 3 cm. in diameter. They may occur following a roentgen-ray burn and in scleroderma. The mat form is from  $1\frac{1}{2}$  to 4 inches in extent. It is vivid pink in color. It may occur in cirrhosis of the liver. Osler has also seen it in a case of leukemia. Generalized acquired telangiectases, telangiectases essentielles en plaques of the French, occur in large numbers over the trunk and extremities as numerous stellate venules. This is a rare form. Stokes found about thirty-three cases. Multiple hereditary telangiectases with recurring hemorrhages is the form under discussion in this paper.

Osler,<sup>2</sup> Brocq<sup>69</sup> and Vidal<sup>20</sup> recognized the rare form of generalized telangiectases or telangiectases circumscripta universalis involving the skin of the trunk, the arms and legs.

Paul<sup>70</sup> reported the first family with this condition from Australia.

A woman, aged 32 years, had had epistaxis since childhood. At about adult life, angiomas appeared, and increased in size and number with advancing years. A dozen or more of bright red angiomatous lesions appeared on each side of the patient's face, varying from a pinpoint to a millet seed in size. The mucous membrane of the lips was extensively involved. The tongue showed numerous angiomas. A few lesions were present on the hard palate and on the conjunctival surfaces of the eyelids. An angioma on the nasal mucous membrane was present, from which hemorrhage frequently took place. This was destroyed by radium, with the result that the epistaxis was greatly diminished. There were also a few telangiectases on the palmar surface of the left hand and on the dorsal surfaces of the fingers.

In spite of the long-continued and persistent attacks of epistaxis, the patient was not anemic. Blood count: Erythrocytes, 5,110,000; leukocytes, 12,200. There was no tendency to hemophilia.

Twenty-one members of this patient's family suffered from the disease, from the greatgrandmother down to the two children of the patient, a boy, aged 3 years, and a girl, aged 7 years. The patient's greatgrandmother, grandmother, grandmother's sister, mother and mother's three brothers and one sister, the patient's six brothers and one sister, and her two children were all affected. These two children had recurring attacks of epistaxis, but no angiomas.

As to the hereditary form with hemorrhages, it is described by Osler, Weber, Hanes and Steiner. In this group of cases the lesions of dilated capillaries are confined largely to the skin of the face and the mucous membranes of the mouth and nose. The tendency to recurring nasal hemorrhages (familial in type) is a prominent feature and there is a hereditary history of recurring hemorrhages and telangiectases in the family. Angiomas of the skin associated with acromegaly have been reported only by Head.

69. Brocq: Ann. de dermat. et syph. 8:41, 1897.

70. Paul, S. N.: Brit. J. Dermat. 30:41, 1918.

The lesions in the hereditary group of cases are more apt to become prominent and increase in numbers between the ages of 35 and 50. Most of these patients suffer from symptoms of a profound secondary anemia. The most common seats of the telangiectases are the cheeks, lips, ears, nose, fingers and tongue. They first appear in the skin or mucous membranes as pinpoint spots, like pinpricks, a little beneath the surface and then they increase in size and become more prominent and darker in color. A fine vascular network may be seen under the skin in some places.

#### DIAGNOSIS

The diagnosis is not difficult. One must avoid the mistake of diagnosing these cases as hemophilia, hemorrhagic diathesis, purpura, scurvy, or pernicious anemia, or the "phthical state with hemorrhages." The clotting and bleeding time is always normal, and there is no history of hemophilia in these cases. The blood platelets are not appreciably reduced, and the erythrocyte resistance remains at the normal level.

#### TREATMENT

Treatment does not confer much relief from the hemorrhages and lesions. Iron, arsenic, calcium salts, thyroid extract and corpus luteum have all been tried with little effect. Osler once gave hypodermically 250 c.c. of a 1 per cent. gelatin solution. Calcium chlorid, 15 grains, three times daily in cinnamon water has been the remedy frequently used by me. As the bleeding seems to become more severe after the fourth decade, we must double our efforts, especially in women reaching the climacteric period, to try to stop the attacks of epistaxis, because of the high strung and tottering nervous system. Sometimes epinephrin, antipyrin solution, or hydrogen peroxid, may check the bleeding. Kephalin, thrombokinas, coagulen, thromboplastin, blood serum, whole blood, or even blood transfusion may be tried.

The chromic acid bead, electric needle, radium and even excision may be resorted to, for some of the telangiectatic lesions. The carbon dioxid stick has been used with some success.<sup>71</sup>

#### SUMMARY

1. A review of the literature on telangiectases of the hereditary type associated with familial epistaxis is given.
2. Thirty-one families afflicted with this disease are on record in medical literature. Several cases are on record which are not alto-

71. Bruck, F.: *Med. Klin., Berl.* **13**:505, 1917.

gether typical of this condition. They have been mentioned in this review, but are not included in the thirty-one cases.

3. No general treatment seems to be effective, owing to the congenital developmental defect of the vascular system inherent in these patients.

4. Local treatment may reduce the number and severity of the hemorrhages and improve the general condition of the patient.

5. Dermatologists, rhinolaryngologists and internists should examine patients who complain of these skin lesions (telangiectases) or recurring hemorrhages more thoroughly and analyze the family histories. In this way some previously undiagnosed or undiscovered cases may be brought to light.

6. A case of hereditary telangiectasia with severe recurring nasal hemorrhages is recorded and cases are mentioned of two married sisters, seven children and the patient's mother, all in the same family, suffering from the same disease, a total of eleven cases in one family.<sup>72</sup>

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72. The following references may also be consulted:

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## SOME FUNDAMENTAL PRINCIPLES OF ELECTRO-CARDIOGRAPHY \*

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There are certain fundamental physical and physiologic principles concerned in the production of the human electrocardiogram, which, if thoroughly appreciated, are sufficient for an analysis of the various normal and pathologic forms of this curve. This paper will concern itself with a brief statement of these principles, their proof and their application in electrocardiography.

1. Lead II = Lead I plus Lead III. This is a law whose proof is found in the law of the conservation of energy. If this principle were not as stated, the law of the conservation of energy would be false and perpetual motion possible.

Leads I, II and III are the expressions of potential differences existing in the heart at any given moment. As these three leads lie in the frontal plane, they represent the frontal plane value of the heart's potential differences; that is, the value of cardiac potential differences situated in any planes of space as projected on the frontal plane.

If we accept Einthoven's schema of the equilateral triangle,<sup>1</sup> and it has been shown that it represents the conditions in the human body with sufficient accuracy,<sup>2</sup> then it is possible from any two leads to find the actual direction of the heart's electric tension as projected upon the frontal plane, the "angle  $\alpha$ ," and to find a value of potential difference which has a definite relation to the actual potential difference in each heart,<sup>2</sup> the "manifest value."

2. When the whole of the heart is in the same state of excitation, then there is no potential difference in the heart and neither Leads I, II or III, will show a galvanometer deflection, no matter what the shape of the heart or its position in the body.

Let us think of a muscle cylinder located in a cylindrical trough filled with physiologic sodium chlorid solution. Electrodes are attached at the ends of the cylinder and the electrodes connected with a galvanometer. If both ends of the muscle are excited over equal volumes of muscle substance, the two volumes of negativity cause equal and opposite potential differences in the muscle and thus counteract one another. The galvanometer will indicate no electrical activity in the muscle. If we now assume that the whole of the muscle is in the same state of excitation, then we can divide the muscle into small vol-

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1. Einthoven, Fahr & de Waart: *Pflügers Arch.* **150**:275, 1913.

2. Fahr: *Arch. Int. Med.* **25**:146 (Jan.) 1920.



umes of substance in such a way that a volume on one side of the center of gravity corresponds in size and position to a volume on the other side. The electronegativity in the one counteracts that in the other, and the galvanometer shows no deflection.

We can think of the heart as being divided into a large number of muscle cylinders parallel to any lead we choose, and as none of these muscle cylinders will produce a potential difference for the given lead when the whole cylinder is in the same state of negativity, we can conclude that when the whole heart is in the same state of electronegativity there will be no indication of potential difference in this lead. In the same way we prove it for all leads, and thus come to the conclusion that when the whole heart is in the same state of excitation, there can be no sign of electrical activity in either Leads I, II or III.

Furthermore, it is now easy to see that the center of gravity of the muscle mass is an important point in the heart for the electrocardiographer. Every point in the muscle substance when excited causes a potential difference of such direction in the heart as would be represented by a line drawn through this point and the center of gravity. This point is negative; the center of gravity is positive. Furthermore, the farther a point is from the center of gravity, the greater the magnitude of the potential difference produced by the excitation of a given volume of muscle substance.

Looking at a frontal section of a human heart as it lies in the chest, it is seen that the greater mass of the subendocardial layers of the conducting tissue lie basally to what must be about the center of gravity of the muscle mass. When, therefore, the excitation process has spread from the main branches of the bundle into the whole of the subendocardial layers of the heart, the vector of potential must have such a direction that the base is negative to the apex. The R peak indicates excess of basal negativity in the human heart, and probably marks the end of the subendocardial spread of excitation fairly accurately.

3. The Q R S group must represent the spread of excitation throughout the ventricles, the T wave must represent the dying out of the excitation. Some have believed that the Q R S group represents the excitation of the muscle, and the T wave the contraction of the muscle. That this view is not in accordance with the facts is shown by the fact that records of the beginning of the intraventricular pressure<sup>3</sup> as well as heart sounds<sup>4</sup> show that they are already established before the Q R S group has ended, and often many 0.01 second before the beginning of the T wave. Moreover, the diphasic action current from

3. Garten: *Ztschr. f. Biol.* 66:23, 1915.

4. Battaerd: *Verdere graphische onderzoekingen over de acustische verschynselen van het hart.* Leyden, Edward Ydo, 1913.

extrasystoles is against this view of the T representing the contraction of the muscle, the QRS representing the excitation of the muscle.

Others have looked on the QRS group as related to excitation and contraction and the T wave as related to metabolic processes. Against this view it may be stated that it is possible to reduce contraction to a minimum thus reducing metabolism and at the same time the QRS, and T retain approximately their normal form and size.<sup>5</sup> I have in my possession records of electrocardiogram complexes QRS and T which were not followed by a pulse at the carotid and not associated with a second heart sound. The T wave in these complexes is as large as the T wave in a preceding or following complex which was accompanied by a pulse in the carotid and a second heart sound. In the first case, the energy developed by the heart is much greater than in the second, and correspondingly the metabolism in the ordinary sense is greater, yet there is no corresponding difference in the T wave.<sup>6</sup> Moreover, it must be urged that in all experimental work on muscle it has been shown that the electronegative wave precedes the contraction wave by only a very short period and dies out, as a rule, only very shortly before the end of the contraction. As the heart contraction begins at about the R peak and ends just after the T wave, it is much more in accordance with the facts of muscle physiology to look on the QRS as the representative of the spread of excitation throughout the heart muscle and the T wave as the dying out of it in the muscle. We know that the rise of negativity at a point in a muscle is very much more rapid than its decline.

4. Measurements of the direction of potential in the heart in so-called "left ventricular preponderance" show that it is actually a preponderance of right sided negativity that determines the peculiar form of the curve, and measurements of the direction of potential in "right ventricular preponderance" show that the forms of these curves are really determined by left sided preponderance of negativity in the heart.<sup>2</sup> It is the length of the path of conduction and the position of the center of gravity of the heart which determines so-called "left ventricular preponderance." It is not the greater negativity of a larger left or right ventricular musculature, as, I believe, Lewis<sup>7</sup> understands it.

I have made some necropsy measurements which support my views. In one case of combined mitral stenosis, mitral regurgitation and relative tricuspid insufficiency the electrocardiogram showed the typical

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5. Noyons: *Onderzoekingen gedaan in het Physiol. Lab. Utrecht*, V Reeks., **11**:208, 1909. Einthoven & Rademaker: *Pflügers Arch.* **166**:109, 1916.

6. Einthoven & Kortweg: *On the Variability of the Size of the Pulse in Cases of Auricular Fibrillation*, *Heart*, **6**:107, 1916.

7. Lewis: *Heart*, **5**:367, 1914.

downward pointing QRS group in Lead I and the high upward pointing QRS group in Lead III. Analysis showed that the vector of potential in the heart pointed to negativity of the *left side* throughout the period of the ventricular electrocardiogram. The musculature of the left ventricle was 50 per cent. thicker than that of the right ventricle but the path of conduction along the right branch of the bundle to a point close to where the bundle breaks up into finer branches was about 1.5-2 cm. longer than the path of conduction along the left branch to the points where it begins to break up into finer branches and become lost for macroscopic vision. Measuring from these points to various points near the bases of the ventricles showed a path in the right ventricle on the average about from 3 to 4 cm. longer than in the left ventricle. Of course, such measurements are very inaccurate. They can only show in a general way that the path of conduction is longer on the one side than on the other. In the same way a necropsy of the heart of a patient who had been supporting a systolic blood pressure of over 200 for years showed a longer path of conduction in the left ventricle than in the right. The electrocardiogram was the typical electrocardiogram of so-called "left ventricular preponderance," and analysis by means of the schema of the equilateral triangle showed that negativity of the right side of the heart determined the form of this typical electrocardiogram of so-called "left ventricular preponderance."

I wish to point out that there is nearly always left ventricular preponderance of musculature even in pure mitral stenosis.<sup>7</sup> Therefore, if the muscle mass was the factor that determined the peculiar form of the electrocardiogram in so-called "right ventricular preponderance" we could only have "left ventricular preponderance" types of electrocardiograms.

5. The analysis of the electrocardiograms of so-called left bundle branch block indicates that the negativity gets into the left side of the heart first, and analysis of the electrocardiograms of so-called right bundle branch block indicates that the negativity gets into the right side of the heart first.<sup>2</sup> In other words, we have frequently been diagnosing bundle branch block on the right side when it really was on the left side, and vice versa. Recently Oppenheimer and Pardee<sup>8</sup> have sectioned the bundle and its branches in cases showing the bundle branch type of electrocardiogram and have confirmed my views on this subject.

6. The electrocardiogram is the expression of the action current. Its form and size depends almost entirely on the way in which the

8. Oppenheimer & Pardee—American Society for Clinical Investigation, Atlantic City, May 3, 1920.

excitation process spreads in the heart. There is no relation between the form and size of the electrocardiogram and the work done by the heart or the reserve power of the heart. When the whole of the heart muscle is excited and in contraction, there may be no electrocardiographic sign of activity as stated in 2. Extrasystoles which are insufficient to throw out blood into the aorta may show the highest curves, or may be exactly like normal ventricular electrocardiograms which are followed by strong ventricular contractions. Powerful hearts may show very tiny QRS groups and small T waves, or they may show large QRS groups and large T waves. For the sake of the clinician who has not made a thorough study of electrocardiography, it should be stated that the electrocardiogram can only answer questions as to the origin and propagation of the excitation process in the heart and can give no direct answer to the question of the contractile efficiency of the heart muscle.<sup>9</sup>

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9. While this paper was in the hands of the editors, a paper on "Bundle Branch Block," by Wilson and Herrmann, appeared in *Arch. Int. Med.*, August, 1920, p. 153. It is too late for me to prepare a long article on bundle branch block, but it is necessary that I come out definitely in opposition to such statements of Wilson and Herrmann, as "To assume that preponderant muscle activity at the apex of the heart must cause a downward deflection in Lead II, or that corresponding activity at the base must cause an upward deflection in the same lead as has so frequently been done; to assume, as Fahr has done, that when the electrical axis as determined by Einthoven's formula points to the left the preponderant muscle activity is on the right side of the heart is totally unjustifiable." This conclusion of Wilson and Herrmann is based on their interpretation of the distribution of potential in the cylinder B, Figure 2, of their paper when the point L is in excitation.

Their interpretation is false, in my opinion. When the point L is in excitation all other points of the muscle mass AMB are positive. There is a potential difference between A and L as well as B and L and M and L. Moreover, muscle experiments show that M is negative to A and B when the point L is in excitation and lies in the same muscle fiber or syncytium of fibers as M. The resultant of all these potential differences must be a potential difference of such a direction that the portion LM of the muscle is negative to the portions A and B. In other words, the potential difference in the cylinder must be such that the electrode S is negative to R. All this follows from the fact that all points on a muscle are positive with respect to the excited points and not just to one point as M. It makes absolutely no difference whether the point L is located in a syncytium of muscle spread over one surface of another syncytium of muscle, or whether the point L is located in one large syncytium. As a matter of fact, I do not believe that the negativity produced in the Purkinje system itself is large enough to affect the galvanometers. Experiments which I have carried out show that potential differences of the order of tenths of volts are concerned in the production of the electrocardiogram. A small flat piece of tissue like the subendocardial Purkinje system would not, in all probability, produce voltages this high.

Furthermore, I wish to point out to Wilson and Herrmann that most of Lewis' dog experiments agree with my interpretation of bundle branch block, and that Oppenheimer's examinations of hearts of bundle branch block certainly do not support the accepted view of bundle branch lesions.

## ACHOLURIC JAUNDICE\*

M. A. BLANKENHORN, M.D.

CLEVELAND

Acholuric jaundice has long been recognized and frequently seen in many conditions with various clinical designations. Most commonly it is ascribed to some disorder of the liver or to anemia, but because no bile appears in the urine little investigation has been made of such jaundice. In 1917<sup>1</sup> I reported an investigation of the blood in pernicious anemia and found that fifteen out of twenty patients had bilirubin in the plasma and none had it in the urine. I concluded from these findings that bile pigment was in some way fixed to the blood plasma and could not be excreted by the kidney. Previously Dr. Hoover and I reported<sup>2</sup> a series of observations under the title of "Dissociated Jaundice," in which it was pointed out that biliary elements occur in the blood in varying amounts; that there is a fairly constant "threshold" for these substances above which they appear in the urine; but that in some conditions, principally diseases of the liver and the anemias, this threshold is quite high. In many subsequent observations, this same thing has been observed, and I have also found both dialyzable and nondialyzable bile pigment in the blood—nondialyzable alone in the milder grades of jaundice, and both dialyzable and nondialyzable in the more severe grades of jaundice. I also reported that, when dialyzable pigment was present in the blood, bile pigment was usually found in the urine; and when no pigment could be dialyzed from the blood, none would be found in the urine. There have been very few exceptions to the rule that bile pigment of the blood diffuses through collodion membrane whenever it goes through the kidney.

This method of study has disclosed many cases of acholuric jaundice, some so faintly jaundiced that a chemical test of the plasma with nitric acid was the only evidence of jaundice, others so very yellow that the absence of choluria demanded explanation. In a very few of the latter cases, impairment of kidney function could be admitted as a possible cause. In others, where no defect in kidney function could be found, it was assumed that something peculiar to the conditions of cholemia determined the retention of pigment. This report,

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\* Read before the Association of American Physicians, May, 1920.

1. Blankenhorn, M. A.: The Bile Content of the Blood in Pernicious Anemia, *Arch. Int. Med.*, **19**:344 (March) 1917.

2. Hoover, C. F., and Blankenhorn, M. A.: Dissociated Jaundice, *Arch. Int. Med.*, **18**:289 (Aug.) 1916.

then, deals with the nature of such bile pigment as could not be dialyzed from the blood plasma and did not appear in the urine.

The specimens dealt with in every case were oxalate plasma free from hemolysis, obtained from patients that were admitted to the medical wards for study and treatment. In every instance the urine was examined for bile and an inspection was made of the skin and sclerae for jaundice. Also, jaundiced specimens of plasma were fabricated in the laboratory by adding various amounts of fresh gallbladder bile to freshly obtained oxalate plasma. It was found that, when sufficient gallbladder bile was added to give the plasma a deep yellow stain, the plasma, when dialyzed in water, would give only a part of the bile pigment, and that prolonged dialysis in running water would not completely decolorize the plasma to its original condition. The amount of pigment thus remaining undialyzable is quite variable. When plasma was stained for a short time by weak solutions of bile, less remained as undialyzable; when stained for longer periods and with stronger solutions, considerably more remained. It was also found that when colorless plasma was placed within the collodion sac, with a dilute aqueous solution of gallbladder bile surrounding the sac, the bile pigment would penetrate the membrane and stain the plasma, but subsequently could not be removed completely by dialysis.

Jaundiced plasma obtained from forty patients was dialyzed into small amounts of water to determine the presence of any dialyzable pigment, and if any was found the plasma was then dialyzed for twenty-four hours in running water, the nondialyzable residue being preserved. In no instance was it possible completely to decolorize plasma by dialysis. But there was quite a wide variation in the amount of undialyzable residue in different specimens.

It was found that when the proteins were removed from plasma by coagulation with heat, the coagulated proteins were stained yellow or yellowish green, and that when only nondialyzable pigment was present, coagulation of the plasma and filtration removed all of the color. In plasma that contained dialyzable as well as nondialyzable pigment, coagulation by heat and filtration did not remove all color. However, after such specimens were dialyzed with running water for twenty-four hours, thus removing all dialyzable pigment, and then coagulated with heat, filtrating would remove all of the color. It was then apparent that nondialyzable bile pigment is associated with the protein of the plasma. When the proteins of the plasma were removed by salting out and were then precipitated, the precipitate was found to be yellow or green, depending on the amount of pigment present.

After complete precipitation by salting out, the filtrate would be entirely colorless and give no biuret reaction. When proteins were salted out fractionally<sup>3</sup> by ammonium sulphate, all three elements—euglobulin, pseudoglobulin, and serum albumin—were found to be pigmented.

Heat coagulated proteins could be washed with water, dilute acids and alkalies without losing any of their pigment. When extracted with alcohol, the pigment was removed quickly and entirely, and could then be identified as bile pigment by the various color tests. No pigment could be removed by prolonged extraction with ether or petroleum ether from ten specimens thus treated. Strong acids or alkalies did dissolve the coagulated proteins and decolorize their added pigment, but they did not extract the pigment unchanged as does alcohol.

Precipitated proteins which are stained by bile pigments behaved in the same manner to solvents, i. e., they gave up their bile pigments only to alcohol, and not to dilute acids and alkalies or to ether and petroleum ether.

When heat coagulated proteins or precipitated proteins were acted on by pepsin, they went into solution readily and still retained their yellow or green color. When dialyzed in this form, a certain amount of bile pigment would dialyze but not until some of the protein, probably peptone, was dialyzed; that is, the undigested protein, together with its pigment, does not dialyze at all, but when acted on by proteolytic enzymes, metaproteins are formed which are more diffusible but which apparently retain their stain of bile pigment. In no instance was any staining substance found in the plasma which could not be coagulated out by heat and precipitated by salting out. It would appear, therefore, that nondialyzable bile pigment in the blood is combined with the proteins by adsorption, like a colloid stained by a dye.

In a previous report, I offered the suggestion that acholuric jaundice might be explained by retention of bile pigments in the blood, but that such pigment was essentially different from that which was readily dialyzed. I was led to believe this by noticing that in obstructive jaundice, which is the simplest type of jaundice, there is very little nondialyzable pigment in the blood; but in diseases of the liver, particularly of long standing, there is usually a large amount of nondialyzable pigment. This suggested that the formation of nonobstructive jaundice was not simply a process of pouring bile pigment into the blood stream, and that the pigment by its elaboration in the liver was of a different nature from pigment found in obstructive jaundice. However, on further study of the various types of acholuric jaundice, this appearance of a different pigment was not substantiated. It was noted, however, that most of the cases of acholuric jaundice have been jaundiced for a long time. When severely jaun-

diced for a long time, there is a large amount of nondialyzable bile pigment; when mildly jaundiced for a long time, there is a less degree. It is quite probable that the retention of bile pigment can be explained as a staining of the blood proteins, and that the degree of stain varies according to the concentration of the stain and the length of time that the plasma is exposed to the stain.



## CORRESPONDENCE

### THE EFFECT OF CERTAIN BLOOD CONSTITUENTS ON PICRATE SOLUTIONS

*To the Editor:*—In a recent number of the ARCHIVES OF INTERNAL MEDICINE Cowie and Parsons<sup>1</sup> report the effect of certain blood constituents on picrate solutions. As a result of their studies, they conclude that creatinin, acetone, diacetic acid and epinephrin react with the picrate solution employed in the modified Lewis-Benedict method for blood sugar determination; and, further, that the reaction given by acetone and by epinephrin, is so intense that these substances become possible serious interfering substances in the determination of blood sugar by the modified Lewis-Benedict method.

The possible interference by creatinin in the determination of sugar in blood by the picrate method has been the subject of frequent comment in the literature, and it is not our purpose to enter into any discussion of this question at the present time. It may, however, be pointed out that in certain bloods (particularly those of advanced nephritis or uremia) creatinin may contribute something toward the blood sugar figures. Except in rare cases, however, this interference can amount to only a few milligrams of sugar per hundred c.c. of blood.

The figures reported by Cowie and Parsons for interference by acetone and by epinephrin are so astonishing, and so contrary to our experience, that we feel they require some comment in justice to the large numbers of workers who have employed the picrate method of sugar determination in the blood.

Cowie and Parsons state that when added in moderate amounts to pure picrate solutions acetone has very little effect on the development of color; that the acetone "blows off" under such conditions. When, however, acetone is added to blood, these investigators find that they can detect a distinct color change in the picrate solution when adding 2 c.c. of a solution containing 0.05 mg. of acetone per hundred c.c. of solution to 2 c.c. of blood. Since only very moderate success was had in detecting glucose added to blood (25 mg. of glucose per hundred c.c. of solution was the smallest quantity they could detect), Cowie and Parsons conclude that the picrate solution is five hundred times as sensitive to acetone as to glucose. Only a moment's reflection is required to show that any such conclusion as this cannot be correct by quite a large margin. Normal blood may contain as much as 1 mg. of acetone per hundred c.c. of blood. If the picrate solution is five hundred times as sensitive to acetone as to sugar, such bloods would show 0.5 per cent. of glucose due to the acetone alone, and in cases of diabetes, where the acetone content of the blood may be very considerably increased, figures of from 5 to 10 per cent. of sugar in the blood would be quite common.

Our own experiments with acetone have shown that the substance affects the picrate solution approximately to the same degree whether the acetone be added to water or to blood. This finding is what we should expect. When added to blood, acetone is not detectable in the picrate method for blood sugar determination until the quantity added exceeds 7 mg. per hundred c.c. of blood. With larger quantities of acetone the effect becomes more marked with each addition so that when 20 or more mg. of acetone per hundred c.c. are added, the acetone has somewhat more effect than an equal weight of glucose.

It is plain from these findings that acetone cannot be regarded as constituting a really serious interfering substance in the determination of blood sugar by the picrate method. In any case, acetone can be removed quantitatively from blood filtrates by boiling for about half a minute. The filtrate should then be cooled before addition of the carbonate, and the determination

1. Cowie, D. M., and Parsons, J. P.: Studies on Blood Sugar: Effect of Blood Constituents on Picrate Solutions. Arch. Int. Med. 26:333 (Sept.) 1920.

carried out as usual. It will be very rare, indeed, that this boiling of the filtrate will have any effect whatever on the blood sugar found, since acetone seldom occurs in appreciable amounts in blood. Only in cases where the urine is rich in acetone bodies would it be worth while to employ the preliminary boiling.

In Table 11 of their paper, Cowie and Parsons report that they can detect an effect of epinephrin when using 2 c.c. of a solution containing 1 mg. of this substance in 4,000,000 c.c. of water. This would mean that the picrate solution would detect 1 part of epinephrin in 4,000,000.000 parts of solution, indicating entrance into a realm of analytical chemistry into which no one hitherto has entered.

We have carried out experiments with epinephrin, making use of fresh solutions prepared from the free base (adrenalin; Parke, Davis & Co.) with the help of a little hydrochloric acid. We also used the Parke, Davis solution of adrenalin chlorid (1:1,000, which contains about five times as much chloretone as adrenalin). The results of our work in this connection are wholly at variance with those reported by Cowie and Parsons. We find that epinephrin has little more effect than twice its weight of glucose on the picrate solution, either in pure solution or when added to blood. Since epinephrin cannot be demonstrated in systemic blood, or is certainly not present in a concentration greater than 1 part in several million, its possible interference in the picrate method for blood sugar is not worthy of consideration.

We can offer no explanation of the discrepancy between our results with acetone and epinephrin and those reported by Cowie and Parsons. We believe, however, that such results as have been reported by Cowie and Parsons in this connection cannot be duplicated in any properly conducted experiments.

STANLEY R. BENEDICT,

EMIL OSTERBERG,

New York.

#### STUDIES ON BLOOD SUGAR: EFFECT OF BLOOD CONSTITUENTS ON PICRATE SOLUTIONS

*To the Editor:*—Our paper on Studies on Blood Sugar: The Effect of Blood Constituents on Picrate Solutions, published in the ARCHIVES OF INTERNAL MEDICINE, September, 1920, p. 333, contained a typographical error, p. 338, Table 11. Heading of first column should read "Size of blood sample," not "water sample."

We should also like to make the following additions:

Reference 4, page 338, after the words "(per liter)" should follow, Van Slyke and Fitz: J. Biol. Chem. **32**:497, 1917.

After the words, "the acetone blows off," page 338, should follow an asterisk with this footnote: "Samples run with 100, 75, 50, 25, 15 mg. to 100 c.c. of water were practically black; no attempt was made to read them." This sentence should be omitted from the asterisk reference on page 339.

A question has been asked as to why we got the readings 0.040 in our blank determinations. This is the point on the vernier at which the solutions became unreadable. When we got to this point the prism was just emerging from the solution. We could not call it 0.000 and we do not believe it is 0.000. We have had blanks read in different departments of the hospital and by different men who always bring in the figures from 0.032 to 0.040. The same thing happens with the creatinin test of Folin where a picrate solution is used. Readings of blanks handed out to technicians as unknowns always come back 0.040 to 0.048. These points are practically unreadable.

We used a Dubosque colorimeter for all our work.

DAVID MURRAY COWIE, M.D.,

JOHN PURL PARSONS, M.D.,

Ann Arbor, Mich.

## BOOK REVIEWS

**PATHOGENIC MICRO-ORGANISMS.** A Practical Manual for Students, Physicians and Health Officers. PARK & WILLIAMS. Assisted by CHARLES KRUMWIEDE, JR. Lea & Febiger, New York, 1920.

This well known textbook appears in its seventh edition. It is now a book of nearly 800 pages, clearly printed on good paper and containing nine full page plates and 214 engraved illustrations, most of which are well selected and well done. It is divided into three parts, Part I dealing with the general characteristics and methods of study of all pathogens; Part II with the detailed studies of individual organisms, and Part III with applied microbiology.

Part III is, in a way, the most distinctive feature of the book. In it are discussed such subjects as bacteriology of milk, water, air, soil, shell fish, etc.; also the application of vaccines and serums, where, under separate headings, these topics for the various infections are treated, as a rule, briefly. This mode of treatment necessitates the separation of subjects, natural units in themselves, and, to some degree at least, is disadvantageous. But it has its redeeming feature in that the discussion of the field of vaccine and serum therapy becomes easily accessible and the various infections may be correlated in respect to treatment.

New data has been inserted in most of the chapters and some chapters have been rewritten entirely. In respect to mass of data presented, this book surpasses most, if not all, other texts. It is well arranged and coordinated.

As one glances through the pages one is struck by the abundant use that has been made of data that has accumulated largely through studies carried on at the Department of Health of New York City. In a way, this is a desirable feature, since it enables the authors to present much first hand information. This statement does not imply that other sources of information have been neglected. On the whole, a fairly abundant bibliography is presented in the text. The authors have made abundant use of information derived from studies carried on during the war. Such subjects as war wounds, anaerobic bacteria and vaccination are discussed in the light of this experience. And the difficult subject of the bacteriology of influenza is presented in a sane and sensible way. It is gratifying to pathologists and bacteriologists to note the increasing number of satisfactory American texts, of which this is one, on the subject of pathogenic bacteria. In marked contrast one cannot refrain from pointing out the general inadequacy of our American texts in the closely related subject of general pathology.

**EPIDEMIC ENCEPHALITIS (ENCEPHALITIS LETHARGICA).** By FREDERICK TILNEY, M.D., PH.D., Professor of Neurology Columbia University; Attending Neurologist, the Presbyterian Hospital, and the New York Neurological Institute; Consulting Neurologist, Roosevelt Hospital, New York, and HUBERT S. HOWE, A.M., M.D., Instructor in Neurology, Columbia University, Assistant Visiting Neurologist the Presbyterian Hospital, New York. Pp. 252. New York. Paul B. Hoeber, 1920.

This book is an expansion of articles by Tilney and Riley (*Neurological Bulletin*, March, 1919) and Howe (*Neurological Bulletin*, May, 1919), with additions and further elaboration of original clinical and pathological material. There is also a general discussion of the various aspects of the disease, based on the authors' cases and reports in the literature. The book contains valuable and original detailed data, but does not give a comprehensive review of the literature of the disease, and the material while rich and described with dependable accuracy—is not as fully elaborated as may be desired by busy readers. There are fifty-three illustrations, many of which are taken from the previously mentioned articles by the same authors.

PASTEUR: THE HISTORY OF A MIND. By Emile Duclaux. Translated and edited by Erwin F. Smith and Florence Hedges. Octavo. Cloth. Pp. 363. Illustrated. Philadelphia and London: W. B. Saunders Co., 1920.

It was an excellent idea of the senior translator to publish this work at this particular time, although the bitter words of Declaux in a letter written in 1882 still have some application. He said: "I know very well that old physicians do not read any more, and when they do read they do not understand. I know that students think only of their examinations, when they think at all." For some years everything except the daily task had to be neglected. Now we should go back to the cultivation not only of technical matters, but of all that gives a wider knowledge of the growth of medical and biologic sciences and of the great men who have had a part in advancing them. Everyone knows that Pasteur was one of the greatest factors in the vast progress of the last fifty years, but what he did and how he did it will always be profitable to recall. His life and his works have been available for some years in the intimate and sympathetic pages of René Vallery-Radot. Professor Duclaux, who had worked from an early day as pupil and as colleague of Pasteur, and whose generous appreciation of the master was based on the most thorough familiarity with his researches, wrote almost wholly with an eye to the technical and scientific aspects of Pasteur's work, so the two books supplement each other. But, the present work has a great advantage over the original French edition. Dr. Smith has put in the form of an introduction of two dozen pages not only a warm eulogy of Duclaux, but also so beautiful a picture of his life and work that the book might well be called the history of two minds, still better, to use the French word which does not seem adequately rendered by "mind," two "esprits." There is also a very useful "Annotated List of Persons Mentioned in This Book," and reproductions of many portraits of Pasteur and of Duclaux. The index is much superior to those usually found in works of this kind. The translation is, as a rule, smooth and accurate, so much so that one notes with surprise the use of "marine salt" for common salt or sodium chlorid. Public libraries, as well as medical libraries, should place the book where it can be seen and read by all classes of readers, for although Pasteur's period is rapidly receding, his influence on biology in general and on bacteriology in particular was far reaching. Unfortunately, the high price of the volume, though not out of proportion to the cost of getting it up, will prevent many who would wish to own it from having that pleasure.

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## THE CARDIORESPIRATORY MECHANISM IN HEALTH AND DISEASE \*

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The most common complaint of the cardiac patient is shortness of breath. For this reason the average physician uses the respiratory response to effort as a measure of the efficiency of the circulation. Nevertheless, the intimate relation existing among circulation, respiration and metabolism is not generally appreciated by members of the profession.

The basis of life lies in the chemical changes which we term metabolism. It is the energy liberated by the oxidation of carbon and hydrogen that maintains the body functions and supplies the forces required for external work. Indeed, the amount of oxygen which the body uses in a unit of time has been found to be the most accurate measure of the energy output.

The oxygen consumed by the tissues must be transported from the lungs to the working cells by the blood. Failure to supply oxygen in sufficient amount to maintain the well-being of the tissues, or to remove the waste products of metabolism, such as carbon dioxide, is the cause of the distress both in the cardiac decompensated patient and in the winded athlete. Without doubt, the most prominent rôle of the circulation is its respiratory function. Lack of oxygen kills the tissues as quickly as many active poisons. Because of this intimate relationship existing among respiration, circulation and metabolism, I have come to consider them as forming a single physiologic system.

Fortunately, each of the functions of this physiologic triad has a certain elasticity, or what has been termed a factor of safety, and minor changes can occur in either circulation, respiration or metabolism without serious effect. Changes in one are compensated for by adjustments in the others.

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\* The Hamilton Biggar Prize Essay, Cleveland Medical Library Association, November, 1919. From the Cardiorespiratory Laboratory, Medical Service, Lakeside Hospital, Cleveland.

THE RELATION OF THE CARDIORESPIRATORY FUNCTION TO  
METABOLISM

In a series of experiments on men doing progressively increasing yet moderate amounts of work, Boothby<sup>1</sup> found that there was an almost strict parallelism in the time volume of the blood-flow, the time volume of the ventilation, and the oxygen consumption per unit of time. If we make the assumption that the tissues are bathed when at rest with blood having the optimal concentration of the respiratory gases, we should expect that the body would attempt to maintain the same optimal concentration for all degrees of muscular work, and Boothby's findings are not surprising. Moreover, we know that neither the blood nor the tissues can store any great amount of the respiratory gases, and hence, the gaseous exchange of the body must be adequate to meet the demands of tissue metabolism, increasing or decreasing in volume with extreme rapidity according to the respective changes in the gaseous demands of the tissues.

At low levels of metabolism, it may be that such a condition obtains, but when the oxygen consumption is increased tenfold, as it may be during great muscular effort, a greater blood-flow than we can conceive as being possible must be present if the tissues are to be bathed with the optimal pressures of the respiratory gases. For example: we found that, while the average resting man uses about 275 c.c. of oxygen a minute, he uses about 1,100 c.c. when walking 3.5 miles per hour; and 2,060 c.c. when running at a rate of 5.5 miles per hour; that is, he uses four times the amount of oxygen when walking and seven and a half times the amount of oxygen when running, at these respective rates. If the volume of the blood-flow and the volume of the alveolar ventilation increased proportionately with the oxygen consumption, the normal resting minute volume of blood would be increased from the generally accepted average volume of 5 liters to 20 liters when the subject was walking, and to 37.5 liters when running, as given above; and the normal resting alveolar ventilation, estimated by me to be about 4.5 liters per minute, would be increased to 18 and 33.75 liters for the respective oxygen consumptions.

It is rational to hold that the concentration of the respiratory gases in the tissues at rest is best suited for the tissues, and that unless the minute volume of alveolar ventilation and the minute volume of blood increase in direct linear proportion to the consumption of oxygen or the excretion of carbon dioxid, the blood leaving the tissues will contain less oxygen and more carbon dioxid than is best for the well-being of the tissues. Figure 1 shows graphically the optimal theoretic relationship of respiration and circulation to metabolism as a curve,

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1. Boothby: *Am. J. Physiol.* **37**:383, 1915.

in which the abscissae represent work in terms of oxygen consumption, and the ordinates the minute volume of the circulation and respiration.

The volume of oxygen consumed and of air breathed during rest and during muscular effort can be measured accurately, but the measurement of the volume of blood passing through the lungs or heart in unit time is difficult and uncertain, since the methods used are indirect ones. Using what is probably the best indirect method for such measurement, Krogh estimates that during extreme muscular effort his systolic output is about 12 liters per minute. In an athlete he found a maximum of 21 liters. Using as a standard the theoretic relationships among circulation, respiration and metabolism, as shown in Figure 1, I found in short experiments on myself that the volume of air breathed was greatly in excess of that theoretically required by the body when about 2,700 c.c. of oxygen were being consumed each minute. Although no measurements were made on the volume of blood passing through the lungs, it is difficult to conceive of the heart as capable of discharging about 50 liters of blood per minute—the amount required theoretically, as shown in Figure 1. Since at this time the heart rate was about 160 per minute, a systolic output of over 300 c.c. would have been required.

Evidently, the volume of air breathed when high levels of oxygen consumption are established is greater than is theoretically required to maintain the resting concentration of the respiratory gases in the blood, while on the other hand, the volume of the blood discharged by the heart is less than the theoretic optimal value.

Certainly, the ability of the heart to increase the minute volume of blood is more limited than the ability of the body to use oxygen or to ventilate the lungs, and the harmony normally existing among circulation, respiration and metabolism at rest may be disturbed by both physiologic and pathologic conditions. For example, in the case just cited, the breathing which accompanied maximal physical effort was disproportionate to the volume of carbon dioxide excreted or the oxygen absorbed as compared with the normal ratio found at rest. Cardiac dyspnea is another instance of the disturbance of this relationship. Here we have evidence that there is a decrease in the mass movement of the blood, but there is only rarely a most moderate increase in the resting metabolism, and the minute volume of air respired is larger than in the normal resting man. The phenomenon of getting out of breath is simply the reaction of the respiratory center to a blood supply which is not adequate to the metabolic needs of the body at the time. In fact, the amount of work which a normal man can do is not limited by his ability to utilize oxygen or to ventilate his lungs, but rather by the ability of the circulation to meet the demands of the tissues for oxygen and for the elimination of carbon dioxide.

In view of the rather limited response which the heart can make to the demands of metabolism, it is well to determine what reserve elements of safety or degrees of elasticity may be present in the metabolic function, the heart's output, the circulating blood, and the respiration to compensate for the heart's feebleness and make possible the maintenance of higher levels of work than we have shown to be theoretically best for tissue well-being.

#### METABOLISM

In order to work, the tissues must be supplied with foodstuffs and with oxygen. A limited amount of work can be done by muscle in an atmosphere of nitrogen, but in this case it is using its stored up energy, and fatigue products, such as lactic acid, collect in the muscle. If oxygen is supplied to such a muscle, it is able to perform a considerable amount of work again without replenishing its carbon supply. There is evidently a small factor of safety in the pent up energy of muscle; supply of oxygen must be furnished it continually and its carbon dioxide removed immediately.

#### THE CARDIAC OUTPUT

The tissues are dependent on the blood which is delivered by the heart for their metabolic exchange. Unfortunately, the methods which have been devised to study this important question of physiology are not well adapted for clinical work, inasmuch as they are so difficult that even to obtain normal results is a great task. The best data indicate that the resting cardiac output is from 4 to 5 liters per minute, and that at most this amount can be increased fourfold, and this only in the case of trained athletes. The result on the volume flow of blood of increasing the heart rate is dependent in the first instance on the venous pressure. Increase in heart rate, without an increase in the venous pressure in large veins and auricles, resulting in better filling of the ventricles, has little or no effect on the cardiac output. The greater the volume of blood delivered to the heart, the greater will be its output. The optimum venous pressure is that which fills the ventricle during diastole to the maximum extent to which the ventricle is able to respond (Starling<sup>2</sup>). As the rate of the heart is accelerated, the inflow of blood can be increased without overfilling the ventricles. When a larger volume of blood is needed, the accessory factors which maintain the flow of blood in the veins, such as hydrostatic pressure, muscular contraction and muscle tone are, therefore, more important.

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2. Starling: *Linares Lecture on the Law of the Heart*, New York, Longmans Green and Co., 1915.



The changes in force and rate of the ventricular contraction, which accompany increased effort, are the means by which the heart is able to deal with the increased volume of blood which is being delivered to it. Such being the case, an increase in the heart rate can be effective in increasing the minute volume of the blood only as long as the length of diastole is sufficient to insure complete filling of the ventricle. It has been found that rates over 150 or 160 do not increase the minute volume of blood.

#### THE BLOOD

In the case of blood there is some elasticity in the amount of oxygen it can deliver to the tissues and likewise in the amount of carbon dioxide it can take up.

The arterial blood normally contains about 18.5 per cent. by volume of oxygen—that is, 18.5 c.c. in 100 c.c. of blood—and it is estimated that the normal resting organism on an average uses 5.5 per cent. by volume in the capillaries. Therefore, the individual has about 13 per cent. by volume of unused oxygen in the blood returning to the lungs. This amount is reserve oxygen, and in case of necessity the organism may use some of it. Theoretically, it would be impossible to raise the oxygen consumption more than three and a third times ( $18.5 \div 5.5 = 3\frac{1}{3}$ ), the normal resting figure, without increasing the minute volume of the blood. However, even under the most extreme conditions, the blood does not lose all of the oxygen in the passage through the tissues. Probably the amount of oxygen which each unit of blood contributes to the tissues never exceeds 13 per cent. by volume, or from 2 to 2.5 times the average amount.<sup>3</sup>

If it is granted that the blood in the capillaries can give up 2.5 times the normal amount of oxygen, then when metabolism is increased 7.5 times, as when running five and one half miles per hour, a blood-flow of 15 liters per minute would be required ( $37.5 \div 2.5$ ). With a heart rate of 120, each systole would need to expel 125 c.c. of blood. This amount may not be impossible in the physically trained man, but it probably approaches the limit of the heart's ability to expand. When work is accomplished which requires ten times the resting consumption of oxygen, certainly the limit of the heart's ability to supply the required blood is reached in most individuals, and such strenuous work is impossible for any length of time.

In the case of carbon dioxide, we have a different mechanism for transportation from that with oxygen. This gas is normally present in the blood in three states, viz., dissolved in water, making the weak

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3. Recent work by Lundsgaard on patients suffering with anemia indicates that in this disease the reserve oxygen may be almost entirely used. *J. Exper. M.* 30:147, 1919.

acid carbonic; combined with sodium to form the carbonates and bicarbonates, and is claimed by some to be loosely combined with protein. The ratio of free to combined carbon dioxide by volume in arterial blood is about 1 to 20. In venous blood the ratio is less. The amount of sodium bicarbonate is not a fixed quantity; it increases, as Zuntz first showed, when blood goes through the active tissues and decreases as blood loses carbon dioxide in the lungs. Hamburger showed that the corpuscles, and to a less extent the proteins of the plasma, are able to absorb chlorin, thus liberating sodium to be combined with carbon dioxide when its pressure in the blood is increased, or to give up chlorin again to form sodium chlorid when the pressure of carbon dioxide is decreased and the acidity of the blood is increased. At low carbon dioxide pressures there is relatively more of it bound with sodium in the blood than at high pressures of carbon dioxide. Superventilation of the lungs will wash out the carbon dioxide of the blood, in which case the combined carbon dioxide will be decreased less rapidly than the free carbon dioxide, whereas, underventilation of the lungs would result in the opposite condition. While the carbonate content of the blood varies considerably with the volume of respiration, the oxygen content is practically uninfluenced.

#### RESPIRATION

Under conditions of rest and normal breathing the pressure of carbon dioxide in the alveolar air of man is maintained at a fairly constant value in each individual, from which it deviates only slightly. These facts were first established by Haldane and Priestley.<sup>4</sup> Campbell, Douglas and Hobson<sup>5</sup> showed that an increase of 2 mm. Hg in the alveolar tension of carbon dioxide is sufficient to double the amount of ventilation of the lungs. Under ordinary conditions of rest, then, the amount of air breathed in a given time is so adjusted as to keep the alveolar tension of carbon dioxide practically constant. Haldane and Priestley also showed that the alveolar tensions of oxygen may be varied widely by breathing atmospheres containing different percentages of oxygen, without sensibly affecting the amount of ventilation of the lungs. Within wide limits, they believe the ventilation of the lungs is regulated by the alveolar tension of carbon dioxide, and is relatively independent of the alveolar tension of oxygen.

Krogh<sup>6</sup> and others have shown that the pressure of carbon dioxide in the alveolar air is nearly equal to that of the arterial blood. It follows, therefore, that the carbon dioxide pressure in arterial blood is relatively constant. This constancy of alveolar ventilation is generally

4. Haldane and Priestley: *J. Physiol.* **32**:225, 1905.

5. Campbell, Douglas and Hobson: *Ibid.* **46**:301, 1914.

6. Krogh: *Ibid.* **40**:271, 1916.

believed to be brought about through the regulation of breathing by the carbon dioxide pressure or hydrogen-ion concentration of the arterial blood acting on the respiratory center. An increase in the carbon dioxide content of the blood raises the acidity and stimulates the center, which causes the volume of respiration to be increased, or vice versa.

The carbon dioxide pressure of the blood leaving the center is in equilibrium with the carbon dioxide of the cells of the center, and it is, therefore, evident that the carbon dioxide pressure of the venous blood leaving the center is the measure of the stimulus of respiration. Any decrease in rate of blood-flow through the center will be followed by an increase in the carbon dioxide content of the blood coming to the center. *The constancy of the carbon dioxide pressure in the alveolar air is, therefore, dependent on a constancy in the rate of blood-flow through the center.* It is more to the point to insist on the constancy of the pressure of carbon dioxide in the respiratory center than to lay so great stress on the constancy of alveolar ventilation and the carbon dioxide pressure of arterial blood, in which the constancy is only dependent on blood-flow, and approximate.

The important point to remember is that the ventilation of the lungs is governed primarily by the pressure of carbon dioxide or the hydrogen-ion concentration in the respiratory center. Oxygen want, according to current teaching, is not important save in influencing the sensitivity of the center.

*A factor of safety in preventing a surcharging of the blood with carbon dioxide in case of a relatively inadequate circulation would lie in the fact that increased ventilation will lower the carbon dioxide of the blood leaving the lungs, making it possible for a less than normal amount of blood to carry away the carbon dioxide formed in the tissues without having the partial pressure of carbon dioxide in the tissues unduly increased.* However, increased ventilation of the lungs would add little to the oxygen which the arterial blood contains, and oxygen want, due to insufficiency of blood-flow, can be coincident with a practically normal carbon dioxide content in the venous blood. *Superventilation can compensate for the inadequate blood-flow only with reference to the carbon dioxide content of the tissues.*

#### INTERRELATIONSHIP OF RESPIRATION, CIRCULATION AND METABOLISM

From the above facts we have the following hypotheses:

1. If the ventilation of the lungs increases proportionately with the intensity of metabolism, we have presumptive evidence that the minute volume of the blood likewise has increased.
2. If the ventilation of the lungs is greater proportionately than the intensity of the metabolism, it is fair evidence that the circulation

of the blood is not adequate in maintaining an optimum carbon dioxide tension in the venous blood.

3. If the tension of carbon dioxide in the venous blood rises proportionately with the tension of the carbon dioxide in the alveolar air, we have fair evidence that the amount of carbon dioxide contributed by each unit of blood passing through the lungs is not greater than normal.

4. On the other hand, if the tension of carbon dioxide in the affluent blood of the lungs rises disproportionately to the tension of the alveolar carbon dioxide, we have fair evidence that the circulation of the blood is not adequate to maintain the optimal concentration of the respiratory gases in the tissues.

In other words, so long as the blood-flow and the respiration vary directly with the carbon dioxide production of the body, the fall of pressure of carbon dioxide in each drop of blood, in its passage through the lungs, is constant. Any decrease or increase in the difference in the carbon dioxide pressure between the affluent and effluent blood of the lungs, providing metabolism remains unchanged, indicates an increase or decrease in the respective volume flows of blood in terms of the physiologic optimum.

These considerations, based on theoretic grounds, led me to perform experiments which I believe throw some light on the problem of the cardiac and respiratory response to work, and the cause of cardiac dyspnea. They also have been the stimuli which have led to the devising of a method for determining the ability of the circulatory and respiratory systems to respond to the demands of the gaseous metabolism of the body, and they furnish a rational test for the functional capacity of the heart based on cardiac output.

#### METHODS OF DETERMINING THE RELATIONSHIP EXISTING BETWEEN RESPIRATION, CIRCULATION AND METABOLISM

In order to determine the validity of these hypotheses, it is necessary to estimate the volume of air ventilating the alveoli of the lungs at levels of oxygen consumption varying from that of rest to that of maximum effort. The percentage of carbon dioxide in the alveolar air at known levels of oxygen consumption must be determined, so that the pressure of carbon dioxide in the blood leaving the lungs may be estimated. Likewise the pressure of carbon dioxide in the affluent blood—i. e., the blood delivered by the right ventricle—must be known for the same respective levels of oxygen consumption.

Such an analysis of the respiration is most difficult. Unlike the circulation, the respiratory function is modified whenever the attention is directed to it. The respiratory rate can be quickened or slowed at

will, providing the ventilation of the alveoli is kept fairly uniform. Putting a mask or a mouthpiece on the average man so disturbs the respiration that, except for study of the oxygen consumption, the results are usually uncertain. In the individual accustomed to respiratory experiments, probably such criticisms do not apply if extreme care be taken. Nevertheless a critical study of the literature bearing on the volume of respiration and the percentage composition of the alveolar gases, fails to impress one with the accuracy of existing methods used in this study. I have endeavored to modify older methods and to devise new ones that are more accurate and applicable to the clinical study of the respiration; but the methods I have used are not above criticism. Because my methods are something of an improvement, but more because by them I have obtained the data which bear on the above hypotheses, I present them here.

The minute volume of the respiration, the rate and depth of respiration, and the volume of the respiratory dead air space must be known in order to determine the volume of the alveolar ventilation. In order to obtain this information I adopted the following procedure:

#### MINUTE VOLUME OF THE RESPIRATION

The expired air was partitioned by valves made of intestinal membrane, which offered the least possible resistance to breathing and which connected with the mouth of the subject by a suitable mask. The expired air was collected in a hundred liter spirometer of the Tissot type, which was counterpoised by an eccentric wheel in place of the syphon attachment used by Tissot. The volume of each respiration, the rate of respiration, and the total volume of air respired in a unit of time were graphically recorded by means of a recording device on the spirometer, which wrote on the smoked paper of a kymograph, the drum of which was the same height as the bell of the spirometer. Each respiration showed on the drum as an upward sloping line and each inspiration as a horizontal mark. The volume of the respiration was the vertical distance between the horizontal lines of inspiration, calibrated from the bell of the spirometer. The time of the observation was marked by a recording clock, and the total number of breaths taken was determined by counting the number of horizontal lines representing inspiration.

The exercise chosen in our work consisted in walking or running on a movable sidewalk, which is run by an electric motor adjusted to various speeds. In some experiments the rowing machine was used. The oxygen consumed for the period of the observation was determined by analyzing the expired air collected in the spirometer and by the usual methods of calculation (Haldane).

## THE MINUTE VOLUME OF ALVEOLAR VENTILATION

The discussion as to the constancy of the dead air space in deep breathing between Haldane, Henderson, Krogh and Pearce and Hoover<sup>7</sup> made further work on this point necessary. The volume of the dead air space is relatively constant at ordinary levels of respiration. It is only when large breaths are taken, as during forced effort in moderate and extreme exercise, that variation in the dead air space is found. In these cases, however, the increase is relatively unimportant compared with the great increase in the alveolar ventilation. Using a new method for the estimation of the dead air space, I have been able to show graphically the variation in the dead air space in two individuals when different volumes of air are respired. The details of this method and the arguments pertaining thereto will be published later.<sup>8</sup>

The importance of this curve representing the variation in the dead air space lies in the fact that, if it be approximately correct, the volume of the dead air space for any given depth of respiration can be determined. This being known, the volume of the alveolar ventilation can be computed by subtracting from the total respired air the volume of the dead air space multiplied by the number of respirations taken for the observation. If the dead space air is known, together with the volume of the expired air, the number of respirations in the time of the observation, and the percentage composition of the expired air, the percentage of gaseous composition of the expired air can be determined by the formula of Bohr, which reads:

$$\frac{(\text{Percentage carbon dioxide in expired air}) \times (\text{Volume expired air})}{\text{Volume of expired air} - \text{Volume of dead space air}} = \text{Percentage carbon dioxide in alveolar air.}$$

In an earlier paper I described a method of estimating the percentage composition of the alveolar air, which is accurate in principle but difficult in procedure. Since I have obtained equally good results by the method described, I feel that, provided the respirations are as deep as 2.5 times the volume of the dead air space, the percentage composition of the alveolar gases can be more accurately determined by calculating, from the percentage composition of the expired air, the volume of the respirations and the estimated dead air space.

## CARBON DIOXID PRESSURE IN ARTERIAL BLOOD

The work of Haldane, of Barcroft, and of Krogh and Krogh has shown fairly conclusively that the pressure of carbon dioxide in the arterial blood is practically that present in the alveolar air. Hence it

7. Pearce and Hoover: *Am. J. Physiol.* **41**:391, 1917.

8. Pearce and Hoover: *Am. J. Physiol.* **52**:472, 1920.

is possible to determine indirectly the pressure of carbon dioxide in arterial blood by determining the percentage composition of the alveolar air.

CARBON DIOXIDE PRESSURE IN VENOUS OR AFFLUENT BLOOD  
OF THE LUNGS

Christiansen, Douglas and Haldane,<sup>9</sup> using the lungs as an aerotometer, determined the composition of the alveolar air after holding in the lungs mixtures of air containing various percentages of carbon dioxide. They found that, when percentages of carbon dioxide in the inspired mixtures were below a certain value, the percentages of carbon dioxide in the end air of the expiration were above those present in the inspired mixtures, while if the percentage of carbon dioxide in the inspired mixture was above this value, the carbon dioxide in the end air of the expiration was less than that in the mixture. They found that the values obtained tended to become constant, and concluded that this value represented the carbon dioxide pressure in the venous blood. They also found that it was impossible to determine the equilibrium point between the carbon dioxide pressure of blood and alveolar air by holding the breath. Boothby and Saniford<sup>1</sup> used this method and obtained results similar to those of Christiansen, Douglas and Haldane. Wardlaw<sup>10</sup> found that the carbon dioxide pressure in the alveolar air when the breath was held did not reach as high a value as it did when the subject rebreathed the air for an equal length of time. Laurens<sup>11</sup> confirmed the work of Wardlaw. Henderson and Haggard<sup>12</sup> found that, by rebreathing the same air for a number of times but with a period of normal respiration between rebreathings, the carbon dioxide content of the rebreathed air tended to reach a fixed and constant value. From these results, we may conclude that the point of equilibrium between the affluent blood of the lungs and the air of the lungs can be reached. If this point is to represent the normal value of the venous carbon dioxide pressure, the time taken for the observation must be less than the time taken for a complete circulation of the blood.

*Criticism of Earlier Work.*—I have spent considerable time attempting to devise a rapid and accurate clinical method of determining the pressure of carbon dioxide in the affluent blood of the lungs. On some points I have been unable to confirm the results of other investigators. For instance, while the subject is at rest, I have found that, if all but the last portion of the expired air be expired and then the breath be held for about twenty seconds, the sample of air taken at the end

9. Christian, Douglas and Haldane: *J. Physiol.* **47**:244, 1914.

10. Wardlaw: *Proc. Linn. Soc. New South Wales* **41**:786, 1916.

11. Laurens: *Am. J. Physiol.* **46**:147, 1918.

12. Henderson and Prince: *J. Biol. Chem.* **32**:325, 1918.

of a forced expiration, in which the remaining complemental air is expired, has a very constant carbon dioxid pressure. In my own case it is  $0.07 \pm 0.001$  atmospheres. Furthermore, this same percentage is obtained when the remaining complemental air is drawn back and forth into the lungs for twenty seconds and a sample of air is taken.

On another subject a slightly different experiment was done. In this case, following a normal inspiration, the breath was held for 40 seconds and then expired, and a sample of the end air was taken. It contained 7 per cent. carbon dioxid. The experiment was repeated with this change, that the subject breathed back and forth into and out of an empty bag, following a normal inspiration from the atmosphere, and at the end of the period a sample of the end of a forced expiration was taken. Seven per cent. of carbon dioxid was found. In fact, I could find no difference in the pressure of carbon dioxid present in the lungs when forced breathing efforts are made and when the air is simply held in the lungs. In order to put this to a further test, following a forced expiration, I inspired 1,600 c.c. of a mixture of 8 per cent. carbon dioxid and air, and in one case held it for ten seconds and then expired slowly, taking samples of air from the tube near my mouth when I had expired 400, 700, 1,000, and to my limit; and in the other case, I took samples of air from the end of forced expiration, following the rebreathing of the mixture each five seconds. The final result was 7 per cent. carbon dioxid in the end air in both cases. I was able to obtain the same percentage of carbon dioxid in end samples of air expired when rebreathing was done into and out of a bag, as recommended by Henderson, each rebreathing being interrupted with a period of normal breathing. In order to obtain this result, it is necessary, however, that the lungs be not superventilated before each breathing. For example, if, in place of a normal inspiration before each rebreathing, an inspiration of twice or more the volume of a normal inspiration is made, the carbon dioxid in the end air of the following forced expiration, no matter how many times the air is rebreathed intermittently, never reaches as high a pressure. This is due to the fact that the deepened inspiration preceding the rebreathing lowers the carbon dioxid pressure in the lung air so much that a longer time than that taken by the experiment is required to build the carbon dioxid pressure of the alveolar air to that of the venous blood. For this reason, in pathologic conditions where hyperpnea is present, Henderson's method may give lower values for venous carbon dioxid pressures than are actually present.

After satisfying myself that the rebreathing of air containing a percentage of carbon dioxid did not change the tension of the final equilibrium point between the affluent blood and the lung air, and



that for a clinical method it was unsafe to use the expired air as the mixture of air with which to determine the tension of the affluent blood, I decided to use the method employed by Christiansen, Douglas and Haldane, but to use a modified technic.

#### METHOD OF ESTIMATING CARBON DIOXID PRESSURE IN AFFLUENT BLOOD OF LUNGS

The apparatus consists of a rubber bag having a capacity of 2,000 c.c., which connects with a manifold, the outlets of which allow samples of air to be withdrawn into Luer syringes. This manifold in turn connects with a three-way stopcock, one opening of which connects with a mouthpiece while the other opening is free. The bag has an opening in it for the withdrawal of samples of air for analysis, and another connecting with a three-way stopcock, which in turn connects with

TABLE 1.—COMPARISON OF RESULTS FROM INSPIRING VARIOUS PERCENTAGES OF CARBON DIOXID IN OBTAINING TENSIONS OF CARBON DIOXID IN EQUILIBRIUM WITH THE AFFLUENT BLOOD OF THE LUNG

Conditions of Experiment	Per Cent. CO <sub>2</sub> in Mixtures of Air Inspired	First Rebreath- ing, per Cent. CO <sub>2</sub>	Second Rebreath- ing, per Cent. CO <sub>2</sub>	Third Rebreath- ing, per Cent. CO <sub>2</sub>
Rest of 5 min. preceding observation....	4.8	6.0	6.3	6.5
	7.2	6.2	6.4	6.65
	7.5	6.72	6.68	6.93
	8.3	6.8	6.95	6.90
	8.9	7.0	6.95	6.95
	9.5	7.0	7.0	7.0
	10.0	7.6	7.50	7.20
	10.4	7.17	7.20	7.15
	12.5	7.50	7.60	7.30
	14.0	8.20	7.80	7.60
Walk of 2' 20".....	15.0	8.00	7.80	7.40
	7.96	7.60	7.60	7.50
Walk of 2' 22".....	10.02	8.17	8.12	8.15
Walk of 2' 18".....	12.5	8.30	8.00	7.98
Walk of 2' 23".....	15.0	8.6	8.35	8.05
Walk of 1' 30".....	10.0	9.0	9.20	9.20
Walk of 1' 30".....	15.0	9.3	9.20	....

Distance walked, 230 yards in each case.

Total time required from the beginning of the preceding forced expiration to the time of taking the last sample varies between 12 and 18 seconds.

two syringes, which are used for filling the bag with a mixture of air and carbon dioxid. The larger of these syringes has a capacity of 360 c.c.; the smaller one is graduated and delivers 100 c.c. Four barrels of air from the large syringe, 1,360 c.c., are metered into the bag, and the proper amount of carbon dioxid to make up the desired concentration of carbon dioxid is metered in by the small graduated syringe. After the subject has reached respiratory equilibrium, his nose being stopped with a clip, he expires quickly and forcibly to his residual air through the open cock; the cock is then quickly turned to connect with the bag, and the mixture of carbon dioxid and air

is drawn into the lungs. There it is held for four seconds and then expired back into the bag, a sample of the end of the expiration being drawn into one of the syringes connected with the manifold. The air is immediately drawn back into the lungs and again expired, another sample being taken. This process is continued till three or four samples of air have been taken. The carbon dioxide content of the two samples of alveolar air thus obtained is then determined by a Haldane gas apparatus. It is surprising with what rapidity equilibrium is established between the mixtures of air in the different expirations.

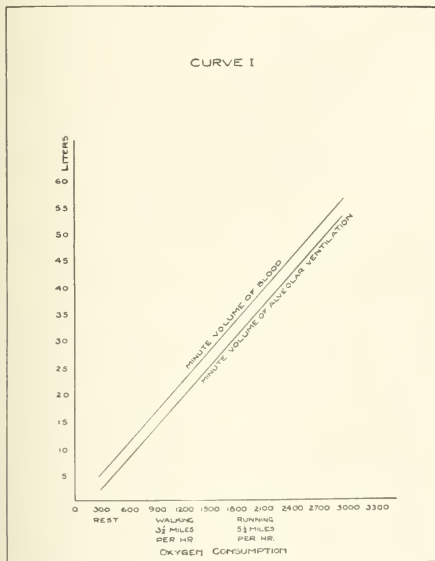
In Table 1 are given the results of an investigation as to the effect of different concentrations of carbon dioxide in the inspired mixture on the equilibrium point of carbon dioxide pressure in blood and alveolar air.

From data obtained by the above methods, we can estimate, indirectly, to be sure, but none the less accurately, the fall in pressure of carbon dioxide which occurs in the blood while passing through the lungs, and the alveolar ventilation at different levels of bodily activity as measured by the oxygen consumption. By comparing the average fall in pressure of carbon dioxide in the blood of the lungs and the alveolar ventilation of the average normal individual at different levels of oxygen consumption, with those obtained in subjects suffering from cardiac or respiratory impairment at the level of their oxygen consumption, we can evaluate the degree of the disability of their cardio-respiratory mechanism.

We have determined the fall of carbon dioxide pressure and alveolar ventilation at different levels of oxygen consumption in normal subjects and also in patients suffering with cardiorespiratory disease. In Table 2 are given the data secured in the case of R. G. P., and H. P., a suspected cardiac case. The significant data in these cases and in a number of others have been graphically drawn in Curves 2, 3, 4 and 5.

In these curves the ordinates represent the minute volume of the ventilation and the percentage of carbon dioxide found in the alveolar air or that in equilibrium with the affluent blood of the lungs. The abscissae represent the oxygen consumption per minute. The minute volume of the alveolar ventilation and the percentage of carbon dioxide found in the alveolar air and that in equilibrium with the blood returning to the lungs when at rest, are considered as being the optimum for maintaining tissue well-being. This being the case, the resting minute alveolar ventilation should be increased 1,000 per cent. when the metabolism is increased 1,000 per cent. The line representing the theoretical optimum based on this standard is drawn as line 1.

Campbell, Douglas and Hobson<sup>5</sup> found that the alveolar ventilation was increased by an amount equal to the original resting minute volume whenever the concentration of carbon dioxide in the alveolar air rose 0.2 per cent. This means, when metabolism is increased 1,000 per cent., providing the blood-flow increases proportionately with the gaseous demands of the body, that there should be an increase of 2 per cent. of carbon dioxide pressure in the alveolar air. The carbon dioxide



pressure of the blood returning to the lungs would also be 2 per cent. higher than at rest. These theoretic optimal values are shown on the curves as lines 2 and 3.

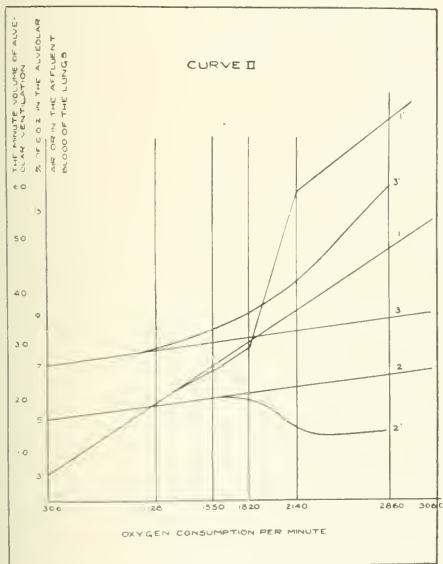
Lines 1', 2' and 3' represent, respectively, the actual minute volume of alveolar ventilation, the alveolar carbon dioxide pressure and the pressure of carbon dioxide in equilibrium with the venous blood found in experiments as given in Table 2.

TABLE 2.—COMPARISON OF ALVEOLAR CARBON DIOXID PRESSURE, THE CARBON DIOXID PRESSURE IN THE AFFLUENT BLOOD OF THE LUNGS  
AND THE MINUTE VOLUME OF VENTILATING AIR AT VARIOUS LEVELS OF METABOLISM, AS MEASURED BY  
OXYGEN CONSUMPTION PER MINUTE

Temperature 18. Barometer 745.

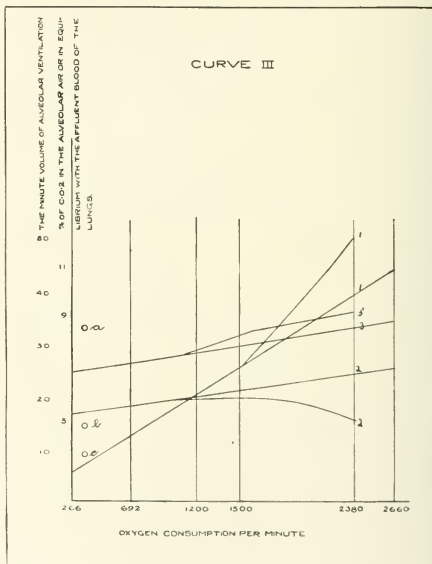
Subject	Oxygen consump- tion % and 760 Mm. Hg	Volume of Respira- tion	Minute Rate of Respi- ration	Volume of Dead Space	Min.-Vol. Expired Air	Min.-Vol. Alveolar Ventila- tion	Per Cent. CO <sub>2</sub> in Expired Air	Per Cent. CO <sub>2</sub> in Alveolar Air	Pressure of CO <sub>2</sub> in Equilibrium With CO <sub>2</sub> in the Affluent (Venous) Blood of Lungs				Respira- tory Quotient
									Per Cent. CO <sub>2</sub> in Expired Mixture	First	Second	Third	
R. G. P.	396	435	16	115	6,940	5,076	3.68	5.05	10	7.2	7.1	7.1	0.75
	348	469	16	115	7,400	5,474	3.90	5.20	10	6.9	7.1	7.1	0.84
	1,158	1,070	29	132	21,300	18,000	5.00	5.70	12	7.9	7.8	7.9	0.94
	1,550	1,050	16	145	26,400	24,080	5.20	5.00	12	8.6	8.6	8.6	0.80
	1,850	1,840	17	178	31,000	27,960	5.30	5.75	12	9.1	9.1	9.1	0.79
	2,160	2,410	25	206	61,000	55,850	4.32	4.73	12	9.6	10.1	10.2	1.12
H. P.	2,860	2,004	38	185	79,500	72,500	4.37	4.89	15	14.3	14.0	14.0	1.69
	966	430	15	130	6,300	4,500	3.82	5.35	10	7.0	7.0	7.0	0.81
	692	870	14	140	11,300	9,320	4.72	5.78	10	7.6	7.5	7.5	0.77
	1,390	1,310	14.5	150	22,000	19,820	5.40	6.00	12	8.1	7.9	7.9	0.78
	1,530	1,780	16	165	28,900	25,560	5.50	6.10	12	8.6	8.5	8.6	0.88
	2,380	2,320	23	195	54,000	50,000	5.00	5.45	12	9.1	9.2	9.3	0.97

The curves show that the ventilation of the lung rises proportionately with the intensity of the metabolism at low levels of metabolism. This confirms Boothby's work.<sup>1</sup> At higher levels of metabolism, however, the minute volume of the alveolar ventilation is disproportionately large. In the introductory pages of this essay we have given the theoretic reasons for believing that the disproportionate increase in the minute



volume of the alveolar ventilation is inferential evidence of a circulation inadequate to maintain tissue well-being. Superventilation of the lungs decreases the amount of carbon dioxide present in the effluent or the arterial blood, which, when passing through the tissues, can take up a larger than the usual amount of carbon dioxide without becoming surcharged.

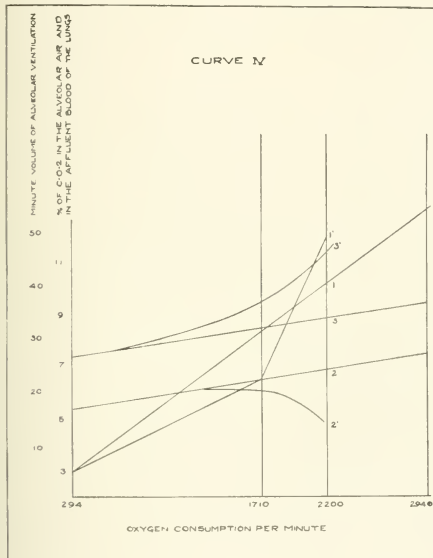
Contributory evidence on this point is afforded by an examination of the behavior of the carbon dioxide pressure in the alveolar air and that in equilibrium with the affluent blood of the lungs at various levels of exercise. As long as lines 2 and 2' and 3 and 3' coincide, we have inferential evidence that the volume flow of blood has varied directly with the gaseous demands of the tissues. When the fall of



pressure between the blood entering and that leaving the lungs is increased above that normally found, it means that each unit of blood is contributing a larger than normal volume of carbon dioxide to the lung air. This fall of pressure is represented on the curves by the perpendicular distance between lines 2' and 3' at any level of oxygen consumption. The greater the fall of pressure in the carbon dioxide

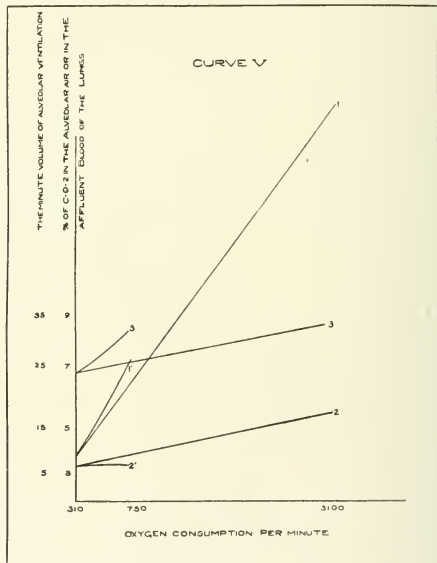
of the blood passing through the lungs, metabolism remaining constant, the less the volume of blood passing through the lungs.

Measurement of the cardiac output can never be based on direct measurement. Here is an inferential method for measuring the relative ability of the heart to maintain the gaseous exchange of the tissues. The volume of the ventilating air is subject to great change, for it



is determined by the balance between the gaseous needs of the body and the transporting facilities which the blood offers to oxygen and carbon dioxide. Circulation, respiration and metabolism represent a physiologic trinity, metabolism being the supreme, but dependent absolutely on the functioning of the others. As long as metabolism, ventilation and circulation vary directly with each other, health and comfort

are found. When they vary disproportionately, they must be said to form no longer a unified trinity, but rather a tragic trilogy. In the experiments cited, comfort and the ability to do sustained work were present so long as metabolism, ventilation and the minute volume of blood, measured inferentially by the pressure drop of the carbon dioxide which occurred in the lungs, varied directly with each other. Hyperp-



nea, faintness, fatigue and inability to do work were present when the ventilation of the lungs was disproportionately great as compared with the metabolism, and the pressure drop of carbon dioxide in the blood passing through the lungs became greater than normal.

In fact, there is apparently no difference, from the physiologic standpoint, between a patient with uncomplicated cardiac incompetence and a man working beyond the ability of the heart to vary its output directly



with the metabolic needs of the body. In the one case the heart's weakness is so great that even the task of living is a strain. In the other, the task of living at a high level of energy output throws a strain on the heart which it is not capable of maintaining for any period of time.

#### THE CARDIORESPIRATORY MECHANISM IN DISEASE

Using this method, I have examined a number of pathologic cardiac conditions, and find that I have secured some rather direct evidence on the relationship of cardiac output to the ventilation of the lungs at known levels of oxygen consumption, as given in the four hypotheses mentioned before.

The length of this paper precludes giving all the data which I have collected in my work. I can present here only a few selected cases which illustrate abnormalities in the cardio-ventilatory mechanism.

In Table 2 and Curve II (Fig. 2) are given the results which I have already discussed.

CASE 1.—R. G. P. (myself), is a man of average physical endurance. He is unaware of having any cardiorespiratory disability. This test applied to about ten soldiers showed that he gave average results. A former prize fighter who was examined was found able to do work requiring 3,000 c.c. of oxygen a minute for nine minutes, and at the end of that time the pressure drop between the affluent and the effluent blood in his lungs was equal to 6 per cent. of carbon dioxid, the same as that present in the case of R. G. P. when using 2,300 c.c. of oxygen per minute.

CASE 2.—The second subject (H. P.), given in Table 2, is a young man, a former Princeton athletic star, who was refused entrance into the army on account of cardiac enlargement and a high blood pressure (Fig. 3). The heart was not enlarged but occupied a low position in the thorax, and the high blood pressure was due to excitement. His diastolic pressure was not increased. A comparison of his curve to that of R. G. P. shows that, if anything, H. P. is able to do a like amount of work with less hyperpnea and a greater cardiac output than R. G. P. (the vertical distance between line 2' and 3', the carbon dioxid pressure in the effluent and affluent blood, is not so great at the same levels of oxygen consumption as in R. G. P.). He was later admitted to the army and served in France one year with the First Division. He presented himself at the laboratory a few days ago and appeared perfectly well.

*The Effort Syndrome.*—The next case is that of a young man who claimed military exemption on account of heart disease, for which he presented his doctor's certificate.

CASE 3.—Physical examination revealed no organic signs of cardiac disease. His pulse was 85 and his respiratory rate was 30 and above, even when at rest. He complained of weakness and faintness on exertion. He impressed one as having the so-called effort syndrome. I found that he was able to do a rather large amount of work, without any indication of failure of his heart to pump the amount of blood necessary to prevent it from being surcharged with carbon dioxid, when it returned to the lungs after passage through the tissues. On Curve 3 is drawn the minute volume of the alveolar ventilation and the percentage of carbon dioxid in the alveolar air and that in equilibrium

with the affluent blood of the lungs at different levels of metabolism. The pressure drop between his affluent and effluent blood (distance between lines 2' and 3') (Curve 4, Fig. 4) is not greater than in the case of R. G. P. or H. P. His respiratory rate, however, was increased to over 50 when doing work requiring 2,200 c.c. of oxygen per minute. This shallow breathing may have resulted in an uneven ventilation of his lungs, as suggested by Haldane, Meakins and Priestley recently, and have produced a relative anoxemia which accounted for his faintness on exertion. The curve shows that, when using about 1,700 c.c. of oxygen per minute, the volume of his alveolar ventilation, in spite of the rapid and seemingly large total ventilation, is less than theory demands (compare line 1 and line 1').

The next case is interesting since it presents one of the shortcomings of the method when applied to clinical conditions which affect the ventilatory function of the lungs.

CASE 4.—Mr. C., a British soldier, who was gassed with chlorin in the second gas attack of the war, had experienced a very checkered military and hospital career. Physical examination failed to reveal any impairment in the lungs, save some moist râles and bronchitis, which was much worse on wet days. The disability was so small, however, that there was doubt whether he was entitled to a pension. Indeed, it had been suggested that he was feigning incompetency to escape further military service. His respiratory response to work was far inferior to that of the normal R. G. P. The minute volume of the ventilation of the lungs at low levels of work compares to that of R. G. P. at high levels. The carbon dioxide pressure in the affluent blood of the lungs did not rise, however, in a proportionate degree, and the percentage of carbon dioxide in the expired air and likewise in the alveolar air, on account of the hyperpnea, was greatly reduced (Curve V, Fig. 5). Evidently there was a great pressure drop in the carbon dioxide of the blood passing through the lungs, but this was not due primarily to the increased carbon dioxide pressure of the affluent blood but rather to the decreased pressure of the carbon dioxide in the affluent blood as modified by the low pressure of alveolar air. How can we account for this condition? It is easily explained on the assumption that the fluid present in some of the fine bronchi and alveoli did not allow free exchange of the respiratory gases to the blood passing through their walls. The blood reaching the left heart was therefore a mixture of blood which has been imperfectly aerated and that which has passed through the walls of normal alveoli and been adequately ventilated. Indeed, the blood which has passed over the normal air sacs was better than normally ventilated; its carbon dioxide pressure was reduced below that normally present, but its oxygen content was not changed, since hyperventilation of the lungs adds little if any to the oxygen which is present in arterial blood. This blood, low in carbon dioxide, reaching the left heart, mixes with the blood which has not been properly aerated in the air sacs full of moisture, and the resulting mixture may be a blood having a normal carbon dioxide content for arterial blood but a low oxygen content. The low oxygen content is due to the fact that, in spite of the hyperventilation, the blood passing over the normal air sacs takes up only the usual amount of oxygen and cannot share with the blood which has not been oxygenated in the diseased air sacs, without itself being under-oxygenated as the result.

*Congenital Heart Disease.*—A cardiorespiratory condition very similar to that which we believe existed in this gassed soldier must be present in cases of congenital heart disease where blood passes from the right to the left heart without being aerated in the lungs. I have

studied three cases of congenital heart disease. In all I have found a large minute volume of air when the subjects were at rest. I also found a low percentage of carbon dioxid in the alveolar air. The pressure of carbon dioxid in the affluent blood of the lungs, however, was practically the same as in boys of the same age.

I believe that these findings give inferential evidence that there was small blood-flow through the lungs, and suggest that blood other than that which has passed over functional lung epithelium is entering the left ventricle. The blood which entered the lungs was more completely freed of carbon dioxid than in the normal boy. This blood left the lungs carrying a full load of oxygen and less than the usual amount of carbon dioxid. On reaching the left heart, it mixed with blood coming from the right heart through the abnormal connection. This blood was venous blood having a high carbon dioxid and low oxygen content. The result of the mixture was a blood probably almost normal with reference to its carbon dioxid content but less than the normal oxygen content.

These subjects had potentially a condition of carbon dioxid acidosis, which they compensated for by overventilating the blood which passes through the lungs, so that the blood which departed from the left heart might have a normal carbon dioxid content. In the case of oxygen no compensation can take place, for the blood leaving the lungs carries all the oxygen it can hold and the mixture of aerated and unaerated blood in the left ventricle is more venous or blue than is normal arterial blood. The boys had no air hunger, but their ability to run and play was more limited than in the normal child.

*Lobar Pneumonia.*—A somewhat similar explanation can be given for the presence of cyanosis in pneumonia, providing the pathologic process which destroys the respiratory membrane and makes the exchange of gas impossible precedes the closing off of the pulmonary vessels. Such a condition would give physiologically the same conditions as are present in congenital heart disease. The blood entering the left ventricle in this case would be a mixture of venous blood from the diseased area and arterial blood from the sound area of the lungs.

The respiratory center, responding to the increase of the carbon dioxid content of the blood, increases the minute volume of air respired and lowers the carbon dioxid tension in the arterial blood. This would tend to make the carbon dioxid concentration of the blood normal, but the oxygen content would be determined by the relative amounts of venous and arterial blood being delivered to the left ventricle. It would always be less than normal, since there is no possible mechanism to increase materially the amount of oxygen which the blood will take up. Such a condition can exist without evidence of air hunger or

respiratory distress as long as the oxygen supply is sufficient. However, cyanosis would be present, since the capillary blood is not saturated with oxygen. As the disease progresses, the circulation through the involved lungs becomes less and less and cyanosis disappears.

In several cases of pneumonia in which cyanosis was present without signs of cardiac impairment or air hunger, I have noted a rather large minute volume of respiration and a correspondingly low percentage of carbon dioxid in the alveolar air. Unfortunately, these subjects were too ill to warrant their breathing mixtures of carbon dioxid for the determination of the pressure of the carbon dioxid in the affluent blood of the lungs. Estimation of the carbonates in their blood plasma by Van Slyke's method did not show a sufficient reduction to account for the increased ventilation on the basis of an acidosis. Oxygen inhalation did not relieve the cyanosis. In the greater number of pneumonias, seen late in the disease and without cardiac impairment, the minute volume of air is not large, and the carbon dioxid pressure in the alveolar air agrees with the plasma carbonates. Cyanosis in these cases is not marked.

Especially interesting is one case which I saw twenty-four hours after the onset of the attack.

CASE 5.—The right base was dull, with high-pitched bronchial breathing. Respirations were 28 to the minute, pulse 115, and temperature 104 F. The man appeared to be very ill, but was able to cooperate with me and was fairly comfortable. He had no signs of cardiac impairment and the blood pressure was 135 systolic and 85 diastolic. The most noticeable thing about him was the intense cyanosis, which was present without symptoms of respiratory distress.

Examination of the carbon dioxid capacity of the blood by the Van Slyke method showed practically a normal blood carbonate reserve, and the alveolar air as estimated by my method gave 37.5 mm. Hg carbon dioxid pressure. His alveolar carbon dioxid determined by my method was 26 mm. The following day his general condition was much worse. The right upper was consolidated, his temperature 105 F., pulse 140, and his blood pressure a little lower. His cyanosis had disappeared. He was irrational, and I could not obtain a sample of air for carbon dioxid determination of the alveolar air. His blood carbonates were, however, the same as the day before.

I believe that, in these cases of pneumonia which I have described, one portion of the blood circulation through the pulmonary vessels consists of blood which has been superventilated, while another portion which passes through the diseased area is unventilated. Therefore the confluence of the total blood in the left auricle gives a mixture of superventilated blood and unrespired blood. This will give a total result of an aortic blood which will have a fairly normal amount of carbon dioxid but a low amount of oxygen. The lack of oxygen is responsible for the cyanosis.

*Bronchial Pneumonia.*—The cyanosis of bronchial pneumonia may be explained on similar grounds. The bubbles of moisture which fill many alveoli prevent the free gas exchange of the blood passing through their capillaries. The air filling these bubbles soon comes into gaseous equilibrium with that of the blood entering the lungs. Thus a condition somewhat akin to that present in congenital heart disease occurs. Hyperpnea will reduce the carbon dioxid pressure of blood passing through the normal alveoli to a point which will compensate for the high carbon dioxid pressure in the blood coming from the edematous alveoli, but cyanosis is present because no such compensating measure can supply oxygen. I have found that the administration of oxygen to such patients will relieve the cyanosis but not the air hunger. Air hunger is caused primarily by the presence of too much carbon dioxid in the blood. Oxygen want is not a very adequate stimulus to the respiration. The reason that oxygen relieves the cyanosis in these cases and not in congenital heart disease or in lobar pneumonia is that in the latter cases the blood passes through an abnormal opening to the left heart, or through alveolar walls completely filled with exudate, and no change of gas is possible. In bronchial pneumonia the breathing of oxygen will change the gas in the bubbles from nitrogen with a pressure of oxygen and carbon dioxid equal to that in the venous blood, to oxygen with the same pressure of carbon dioxid as was present with the nitrogen. This high pressure of oxygen is sufficient to oxygenate the blood passing over the alveolus and the cyanosis is relieved. However, no subjective relief is noted, since the carbon dioxid exchange is not altered.

From these it is quite evident that analysis of the cardiorespiratory phenomena by the methods proposed fails to give accurate information concerning the volume output of the heart in cases where the lung as a whole does not serve as a perfect and complete tonometer. In spite of this, valuable inferential evidence as to the amount of blood actually passing through the functional lung is obtained.

*Cardiac Decompensation.*—In several cases of uncomplicated cardiac disease in which decompensation was present, I have found that the minute volume of the ventilating air has been greatly increased, and that the percentage of carbon dioxid in the affluent blood of the lungs, as taken by the method we propose, was a little raised. The metabolism of such patients was not increased more than from 15 to 25 per cent. above the normal resting value. In these cases there was no marked lowering of the total blood carbonates, and as the heart compensated by rest in bed and treatment, the minute volume of the ventilation, and the pressure of carbon dioxid in the alveolar air and that in equilibrium with the affluent blood of the lungs, again approached normal.

CASE 6.—A Mr. M. was admitted to the wards complaining of shortness of breath. He had some air hunger on moderate exertion. Physical examination showed a dilated right heart, an enlarged left heart and pulmonary insufficiency. The diagnosis was syphilitic aortitis and myocarditis and pulmonary insufficiency.

His volume of alveolar ventilation at rest was 12 liters per minute. His oxygen consumption was 276 c.c. per minute. The carbon dioxide in his alveolar air we estimated at 25 mm. Hg. His blood failed to show evidence of acidosis, while his alveolar air indicated that it was present. His venous carbon dioxide pressure, as determined by our method, was 58 mm. Hg. The wide difference between the pressure of carbon dioxide in his arterial and his venous blood indicates that the blood which was passing through his lungs was being superventilated. In this patient the blood entering the lungs bore a little more than the normal resting load of carbon dioxide, but it left the lung with a less than normal amount of carbon dioxide. It entered with a carbon dioxide pressure of 58 mm. and left with a carbon dioxide pressure of 25. Since his blood was approximately normal in its capacity to carry carbon dioxide, we may compute from the above data, together with a determination of his total respiratory exchange, the minute blood-flow through his lungs from the data furnished by Christiansen, Douglas and Haldane<sup>9</sup> on the relationship between the oxygen and carbon dioxide content of the blood. Each 100 c.c. of blood which passed through this man's lung lost at least 12 c.c. of carbon dioxide. The normal figure given by most authorities is 6 c.c. This figure, taken together with the total carbon dioxide eliminated by the patient per minute, which in this case was a normal figure, gives him a minute cardiac output of about 3 liters, which is about half the calculated normal figure.

Because of the small amount of blood which passes through the respiratory center, the metabolism of the respiratory center itself would cause the tension of carbon dioxide to be raised above a normal level unless the blood entering it is capable of carrying away more carbon dioxide than it does under normal conditions.

On Curve III (Fig. 3) are drawn as circles the relationship found among the minute volume of the alveolar ventilation (Circle B), the pressure of carbon dioxide in the alveolar air (Circle C) and the pressure of carbon dioxide in the affluent blood of the lungs (Circle A) at the resting metabolism of this patient. The linear distance between Circle A and Circle C represents a pressure drop of 33 mm. in the carbon dioxide pressure in the blood, while passing through the lungs, whereas the normal carbon dioxide pressure drop in the blood passing through the lungs is 14 mm., which is represented by the linear distance between line 3 and 2 on this curve. The minute volume of the respiration in this case was twice that of the normal resting individual and in spite of this increased ventilation there was a marked increase in the carbon dioxide pressure in the affluent blood of the lungs and in the tissues of the body. In this case, the cardiac dyspnea was undoubtedly due to a carbon dioxide storage in the tissues and may be termed a carbon dioxide acidosis, the difficulty being due to inadequate volume of the blood flowing through the tissues.

This paper has been withheld from publication for more than a year because Dr. R. W. Scott, a former colleague of mine, believed he had good evidence that the carbon dioxid content of arterial blood in cardiac decompensated cases in spite of the hyperpnea, which was present, was greater than normal. This corresponds to Peters' belief that the cause of cardiac dyspnea is the failure to establish an equilibrium between the carbon dioxid pressure in the affluent blood in the lungs and the alveolar air. Dr. Scott recently informed me that he had, by direct analysis of the arterial blood in six uncomplicated decompensated heart patients, obtained quite contrary findings and that he believed he had evidence that there was no difficulty in the establishment of an equilibrium between the carbon dioxid pressure of the affluent blood of the lungs and the alveolar air. Inasmuch as the use of indirect methods which I have employed in my work depends on the blood of such an equilibrium to be established, I wish to express my thanks to Dr. Scott for clearing up this point.

*Pulmonary Stenosis.*—I saw an interesting case of pulmonary stenosis in consultation with Dr. Christie.

CASE 7.—The lad was 16 years old. For the past three years he had noted that he was short of breath when he exerted himself, and he never could play like other boys on account of his lack of wind. He had a dilated right heart, but little, if any, increase in the size of the left heart. He had a marked pulsation over the base of the heart. He was a little cyanotic, especially about his lips and nostrils. The results of his cardiorespiratory examination are given in Curve V (Fig. 5). He had a drop of 3.6 per cent. in the carbon dioxid pressure of his blood while passing through the lungs, and a large resting alveolar ventilation. The average normal drop in carbon dioxid pressure in the lung I believe was about 2 per cent. His inability to exercise was due to his heart being unable to increase the volume of blood which is required. This is shown by the fact that, when he was walking about  $2\frac{1}{2}$  miles an hour, the drop in pressure of the carbon dioxid in his blood passing through the lungs was 5.3 per cent. of an atmosphere, and his minute volume of air respired was also disproportionately great for the intensity of metabolism.

*Auricular Fibrillation.*—It was impossible to secure data on this man when taking moderate exercise. I feel certain that effort would have shown his heart not capable of much compensation.

CASE 8.—This patient had suffered from cardiac disease for years. At the time of the examination his heart was fibrillating, but the patient was very comfortable. He respired 9.5 liters per minute. His alveolar air contained 4.4 per cent. carbon dioxid, and the blood entering the lungs contained a pressure of carbon dioxid equal to 7 per cent. of an atmosphere. The drop of carbon dioxid pressure in the blood passing through the lungs was a little greater than normally found—2.6 in place of 2 per cent.

*Anemia.*—A case of congenital hemolytic jaundice was studied by the method I have developed, with interesting results.

CASE 9.—The blood count was 2,500,000. A loud venous hum could be heard over the jugular vein. The cardiorespiratory function, however, was apparently not disturbed, for he breathed a normal minute volume of air, and the drop of pressure in the carbon dioxid of the blood passing through the lungs was normal for the level of metabolism studied.

This observation confirms the statement of Lundsgaard that in anemia the blood-flow is not affected when the anemia is not too severe.

*Hypothyroidism.*—One case was studied.

CASE 10.—A woman who had suffered from exophthalmic goiter for a number of years came to the hospital for a study of her basal metabolism. It was found that she had a subnormal metabolism. Other features of the case led me to diagnose the case as a moderate case of thyreopriva. The minute volume of air was reduced, being 4.6 liters per minute. The basal metabolism was 27 calories per square meter of body surface, a reduction of about 30 per cent. from normal. The percentage of carbon dioxid in the alveolar air and in air in equilibrium with the affluent blood of the lungs was normal. In other words, there was apparently a blood-flow adequate to maintain the metabolic needs of the body, and the cardiac output was depressed in exact ratio with the metabolism.

*Exophthalmic Goiter.*—In the case of a young man previously operated on for exophthalmic goiter, we found evidences of a larger oxygen consumption at rest than is found in the normal man, and a normal drop in the pressure of carbon dioxid in the blood passing through the lungs. Evidently the blood flow in this case was increased proportionately with the metabolism.

The analysis of ventilation of the lungs with reference to the volume of the blood-flow and the intensity of the energy metabolism has great possibilities, as can be seen by the short list of cases presented.

#### SUMMARY

It is shown in normal men that the volume of alveolar ventilation and the volume of oxygen absorbed increase proportionately at moderate levels of physical exertion. We have given inferential proof that the volume of the cardiac output likewise varies directly with metabolism and alveolar ventilation at moderate levels of work. At levels of work in which the cardiac output is less than theoretically demanded, the factors of safety found in gaseous carrying power of the blood, the increased venous pressure due to increased tone of muscles, etc., and the power of the body to superventilate the lungs—come into play. When these added factors can no longer compensate for the disproportionately small bloodflow, effort cannot be sustained, and a lower level of body activity must be found. A patient suffering from cardiac disease or pneumonia, or the congenital cardiac subject, or any individual having an impairment in his cardiorespiratory function, is living at the expense of one of the factors of safety which



nature has provided for times of physical stress. These patients are, therefore, continually living, as it were, at an energy-output level, with reference to their cardiorespiratory function, equal to that of a normal man while at work. The incapacity of such patients to do hard or sudden work is, on these grounds, quite understandable.

This study of the cardiorespiratory metabolic function had as its prime object the development of methods which might be used in the clinic for the interpretation of cardiorespiratory disease.

The method developed is still poorly adapted for general clinical work, but nevertheless, has given us data which affords a broader viewpoint of the subject of cardiorespiratory dynamics. It has emphasized the importance of the singleness of the function of the circulation and respiration in the nutrition of the body and has shown the need of a closer appreciation of the fact in the teaching of the normal and pathologic physiology of these systems.

A NOTE ON THE EFFECT OF IRRADIATION OF  
THE SUPRARENAL REGION IN RABBITS  
WITH ROENTGEN RAYS \*

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It was early noted that the roentgen ray has a remarkable effect on lymphoid and endocrine tissue. So far as the latter is concerned, the use of the roentgen ray has been confined largely to the thyroid and thymus. In this study we have attempted to determine the effect on the suprarenals of irradiation of the suprarenal region in the intact animal.

The first work on this subject was carried out under the inspiration of Vasquez, who believes that hypertension is probably an evidence of increased adrenal activity and the investigations of his school have been made with this point in view. Zimmern and Cottenot<sup>1</sup> studied four patients with hypertension, whose systolic pressure as recorded by the Pachon apparatus was over 220 mm. of mercury. They then exposed the suprarenal region of these patients to roentgen rays, giving from three to fourteen exposures, and noted that the pressure fell and remained at a lower level for a considerable period. However, they give no details of technic.

Eisler and Hirsch<sup>2</sup> studied the effect of the roentgen rays on the suprarenals of rats. They were able to kill their animals by repeated, closely spaced doses of from 150 to 200 X Kienböck units in from eight to ten days. Except for a slight loss of weight and fatigue the animals presented no symptoms up to their death. At the necropsy, the suprarenals were macerated in physiologic sodium chlorid solution, and their epinephrin content was determined by the blood pressure method. They found that the epinephrin content was reduced in the treated glands.

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\* From the Laboratories of Roentgenology and Internal Medicine of the University of Michigan Hospital.

1. Zimmern, A., and Cottenot, P.: Modification de la pression arterielle chez l'homme par l'exposition aux Rayons X de la region surrenale, *Compt. rend. Soc. de biol.* **72**:676, 1912.

2. Eisler and Hirsch: The Influence of Roentgen Rays on the Suprarenal Capsules, *Verhandl. d. deutsch. Röntgengesellsch.* **9**:104, 1914.

In the present study we have attempted to reach the suprarenals of intact rabbits with a "hard" type of roentgen ray both by irradiation through the anterior abdominal wall and from behind. The right suprarenal lies at the level of the first lumbar vertebra almost in the midline, and is fairly fixed in position by the overlying vena cava and the hepatic ligaments. The left suprarenal lies in loose areolar tissue at the level of the second lumbar intervertebral disk about one inch to the left of the spine and is quite movable.



Fig. 1.—Section of suprarenal cortex from Rabbit 1x showing localized infiltrations of small round cells.

The ray used in every case was that delivered by a standard Coolidge tube on a current of 5 milliamperes, with a 9 inch back-up spark gap, and a 12 inch target object distance. Varying exposure times were used, but in every case the animals were kept saturated at various doses for a week or a week and a half by the method of Kingery.<sup>3</sup>

3. Kingery, L. B.: Saturation in Roentgen Therapy: Its Estimation and Maintenance; Preliminary Report, *Arch. Dermat. & Syph.* **1**:423 (April) 1920.

The suprarenals were examined from one to forty-six days after the last dose. Some of the animals were given the initial dose divided between the anterior and posterior routes and the subsequent doses alternately between these routes. Others were given by one route only. Care was taken to protect the rest of the animals from the ray by means of lead foil and sheet lead.

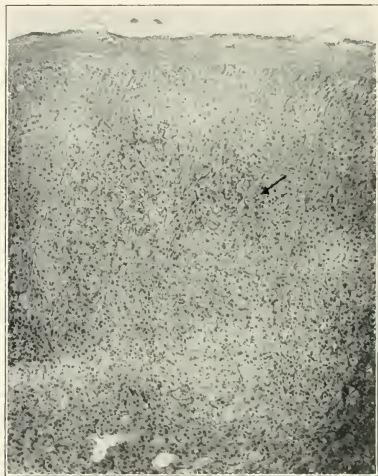


Fig. 2.—Section from suprarenal cortex of Rabbit 1x showing simple necrosis, nuclear pyknosis and vacuolization of the protoplasm.

A few of the animals died, as noted in the protocols, but the majority were killed by a blow on the head. All were immediately necropsied and the weights of the suprarenals, heart and kidneys were recorded. In no case did the latter two organs appear abnormal, nor did their weights deviate from the average normal. The weights of the suprarenals are recorded in the condensed protocols (Table 1).

Rabbits 1x and 51 died within two days after irradiation. Rabbit 37 was found dying twenty-one days after the last irradiation and

was immediately killed. All three animals showed a striking increase in the weight of the suprarenals, and in each case histologic evidence of cell destruction, most marked in the cortex, was obtained. The suprarenals of Rabbit 1x were apparently affected directly (Figs. 1 and 2) and death resulted the day following exposure. Preceding death this animal showed marked retraction of the abdomen, the hind legs were drawn up and there was considerable diarrhea. In the remaining seven animals no histologic changes in the suprarenals were noted but all of the treated glands were relatively heavier than those of the control animals, the greatest increase being found in the three showing microscopic changes. As a general rule, the animal receiving the largest doses in "milliseconds" tended to show the greatest increase in relative suprarenal weight. Many other factors must be considered, such as the saturation dose, the time elapsing between the last dose and the necropsy, the direction of the exposure and, perhaps, most important of all, the marksmanship. As to the latter, the difficulties are great. When both glands are to be exposed simultaneously, the total area to be covered is a diagonal band one inch wide and two inches long. The suprarenals lie at the extreme ends of this band. This area is covered by the ray emerging from a cone with a circular aperture one inch in diameter. Slight movement of the animal on the board or an unusual position of one or the other suprarenal (such variation occurs more frequently on the left) would suffice to cause one of the glands to be completely missed by the direct ray. When the anterior route is used, the difficulty of placing the animal squarely on its back increases the chance of missing the mark. In this route absorption of the ray by the soft tissues of the abdomen is also a factor.

In another series of the six rabbits (Table 2) we attempted to expose one suprarenal to the ray and exclude the other. In this we met with but doubtful success. However, in Rabbit 69 the suprarenal on the side rayed showed slight degenerative changes which were absent on the other side. In a series of twenty-five rabbits not exposed to the roentgen ray the left suprarenal was found to average 23 mg. heavier than the right. The left suprarenals from the three rabbits in which the left gland was irradiated averaged 45 mg. heavier than the right; in the three animals in which the right gland was irradiated, the left suprarenals averaged 29 mg. heavier than the right. The suprarenals of Rabbit 67, which unfortunately had undergone considerable postmortem change when the animal was found that histologic studies were impossible, were definitely overweight and the left suprarenal (the side irradiated) was 95 mg. heavier than the right. This difference, furthermore, is greater than was seen in any one of the twenty-five animals from which the average difference was based.

TABLE 1.—DATA ON TEN RABBITS IN WHICH THE SUPRARENALS WERE IRRADIATED BY BOTH ANTERIOR AND POSTERIOR ROUTES

No.	Dates of Ex- posure	Dose in Milli- seconds	Route	Total Milli- seconds	Satura- tion Dose	Total Ex- posures	Date of Death	Cause of Death	Initial Weight in gm.	Weight at Death in gm.	Weight of Supra- renals in Mg.	Appearance of Suprarenals	Remarks
1-X	2/ 5/20 2/ 5/20	450 450	Ant. Post.	900	900	2	2/ 6/20	—	1,524	1,524	8.5	Cortex: Patchy areas of nuclear pyknosis; numerous small cell inclusions with fragmentation of nuclei; vacuolization of protoplasm with loss of staining ability; at lower microscopic subcortical hemorrhage; patchy medulla with clear pyknosis in medulla such as seen in cortex. Sudan III: Many areas in which lipid content markedly diminished and granules broken up (Fig. 1)	For some hours before death showed marked diarrhea and retraction of the abdomen; hind legs were drawn up during this period
20	2/16/20 2/16/20 2/30/20 2/28/20	450 450 450 450	Ant. Post. Ant. Post.	1,800	900	4	2/25/20	Proe- monia	1,508	1,154	265	Normal.	Rabbit had a deep ulcer on nose which completely healed before death
37	2/16/20 2/20/20 2/23/20	450 225 225	Ant. Post. Ant.	900	450	3	3/15/20	Killed	2,070	1,350	725	Cortex: Macroscopic pin point not- tling in both; diffuse nuclear pyk- nosis of moderate degree; areas of simple necrosis with infiltration of eosinophils; slight protoplasmic vacuolization. Medulla: scattered pyknotic nuclei; otherwise not abnormal.	Found dying and immediately killed; no gross pathol- ogy seen
39	2/20/20 2/20/20 2/23/20	675 675 675	Ant. Post. Ant.	2,025	675	3	3/ 4/20	Early proe- monia	2,515	1,030	595	Cortex: Diffuse nuclear pyknosis; very slight protoplasmic vacuoliza- tion. Medulla: Scattered pyknotic nuclei; otherwise not abnormal.	First dose was given over the entire ab- domen as animal struggled and head fell; retraction slipped off
27	2/16/20 2/20/20 2/23/20	450 225 225	Ant. Post. Ant.	900	450	3	2/28/20	Proe- monia	1,812	1,295	475	Normal.	No gross pathology seen
50	2/20/20 2/23/20 2/23/20	675 375 375	Post. Ant. Ant.	1,050	675	2	4/ 6/20	Killed	1,059	1,550	570	Normal	
51	2/20/20 2/23/20 2/23/20	675 375 375	Post. Ant. Ant.	1,050	675	2	2/25/20	—	2,034	1,504	635	Cortex: Slight nuclear pyknosis; some vacuolization of protoplasm; moderate congestion. Medulla: A few hemorrhagic areas	
52	2/20/20 2/23/20 2/23/20	225 110 110	Post. Ant. Ant.	335	225	2	4/ 6/20	Killed	1,779	1,540	275	Normal	
53	2/20/20 2/23/20 2/23/20	225 110 110	Post. Ant. Ant.	335	225	2	2/23/20	Killed	1,989	1,779	293	Normal	
54	2/20/20 2/23/20 2/23/20	450 675 600	Post. Ant. Ant.	1,725	1,125	3	3/23/20	Killed	2,114	1,862	295	Normal	

TABLE 2. DATA ON SIX RABBITS IN WHICH THE SUPRARENALS WERE IRRADIATED BY THE POSTERIOR ROUTE ONLY

No.	Dates of Ex- posure	Dose in Milli- seconds	Total Ex- posure	Satu- ration Dose	Total Ex- posure	Date of Death	Cause of Death	Initial Weight in Gm.	Weight at Death in Gm.	Side Ex- posed	Weight of Suprarenals in Mg.			Macroscopic Appearance of Suprarenals	Remarks
											Right	Left	Total		
65	4/27/20 5/3/20 5/7/20	300 300 150	3	300	3	6/15/20	Killed	2,700	2,410	R	220	240	460	No sections.....	6/14/20. Had Bitten of young
66	4/27/20 5/3/20 5/7/20	300 300 150	3	600	3	6/15/20	Killed	2,281	2,050	R	190	185	375	Both normal	
67	4/27/20 5/3/20 5/7/20	300 300 150	3	300	3	6/2/20		2,332	2,050	L	950	345	505	No sections	
68	4/27/20 5/3/20 5/7/20	600 600 300	3	600	3	5/19/20		2,675	1,700	L	230	235	465	Right: Some vacuoliza- tion of protoplasm of cortical cells; nuclei stain rather poorly Left: Vacuolization of protoplasm of cortical cells; nuclei stain poor- ly; much congestion of blood vessels Right: Nuclei strongly stained in several areas; slight pyknosis with some vacuolization of protoplasm Left: Normal	Bitten in several places on flank; found dead; some postmor- tem change
69	4/27/20 5/3/20 5/7/20	900 900 450	3	900	3	6/15/20	Killed	2,308	1,965	R	225	265	490		
70	4/27/20 5/3/20 5/7/20	900 900 450	3	900	3	6/15/20	Killed	1,958	1,900	L	230	255	485	Both normal	

It would appear, therefore, that in the roentgen ray we have a method which may prove of considerable service in the study of suprarenal function. Unfortunately, we are unable at present, or in the near future, to continue this work, and consequently submit the data we have obtained for the use of those who may be interested in this line of investigation.

Grateful acknowledgement is made to Dr. C. V. Weller of the Department of Pathology for the preparation of the sections and microphotographs.



## THE TENDENCY OF CARCINOMA OF THE PANCREAS TO SPREAD BY BLOOD-VASCULAR INVASION \*

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Although carcinoma of the pancreas is a relatively uncommon disease, four cases of this condition have been found at necropsy at the Peter Bent Brigham Hospital during a six months' period, including last winter. These cases represent one-half the number of such cases coming to necropsy in this laboratory since the opening of the hospital in 1913, the total being only eight cases. Study of the series shows that in three cases the head was involved primarily; in one case the head and body was involved, in three cases the cancer was diffuse throughout the organ, and in one case it was limited to the tail. Two of the carcinomas were of the scirrhus type, five were adenocarcinomas and one, composed of atypical cells, was interpreted as having arisen from the islands of Langerhans rather than from ducts or parenchyma.

Extensive metastasis occurred in six of the eight cases, a relatively high percentage, judging from the figures obtainable from the literature. In the standard works metastases to the liver and retroperitoneal lymph nodes are usually mentioned, and by some authors they are stated to be common, but there appears to have been little reported concerning more distant secondary growths, and no emphasis has been placed on the notable tendency of these tumors to spread by way of the blood stream.

Baldwin,<sup>1</sup> in a review of fifty cases collected from the Index Medicus up to 1900, finds that scirrhus carcinoma is the most common carcinoma of the pancreas and that metastases are not common, except in the liver. He gives the following figures relative to the frequency of secondary growths in his series:

Metastases: None in 10 cases; liver, 11; neighboring lymph nodes, 11; duodenum, 5; lungs, 3; kidneys, 3 (once in the right kidney and once in the left kidney alone); spleen, 3; capsule of spleen, 1; opening of common duct into duodenum, 2; omentum, 2; pleura, 2; colon, 2; solar plexus and nerves, 2; mesocolon, 1; muscular coat of intestine, 1; abdominal wall, 1; pyloric wall, 1; opening of cystic duct from gall-bladder, 1; psoas muscle, 1; no statement concerning metastases, 8.

\* From the Pathologic Laboratory of the Peter Bent Brigham Hospital, Boston.

1. Baldwin, F. A.: Phila. M. J., 6:1195, 1900.

He does not state, however, in how many instances lesions in various organs were associated in the same person or what combinations were found.

In connection with blood-vascular invasions, Baldwin describes the following condition found in the primary growth in one of his own cases:

Some of the vessels have their lumen completely obliterated by growth into it of tumor cells and others have their lumen partially or wholly closed by laminated thrombi and when these are examined one finds places where two, four, or six cells are seen which are entirely surrounded by fibrin and blood cells of thrombus. If one follows back along the vessel wall, one sees a place where the wall has been involved by tumor from without. First there has been an invasion of the adventitia. From this coat, tumor cells have proceeded along lymph spaces into media and intima. Then points are seen where tumor cells have broken through into the intima and grown into the lumen. It is in these vessels that the laminated thrombi are found in which the loosened cells are noted.

In the series studied in this laboratory, the two cases which on microscopic examination proved to be scirrhus carcinoma showed no metastases, but in the remaining six cases, secondary involvement of the liver was present in all, and regional lymph nodes were affected in all but one.

The lungs of five of the six patients were involved, the stomach was involved in four and the duodenum in four cases, the two latter organs apparently by direct invasion rather than by metastasis, although it was frequently impossible to determine definitely which type of extension had occurred. In three cases there were metastatic foci in the suprarenals and in a fourth case direct invasion of the left suprarenal occurred. The brain was examined in only two cases; secondary growths were found in both. In these two cases, which will be described more in detail later, there was a generalized carcinomatosis, involving almost every organ.

The features on which it is desired to lay emphasis are: (1) the tendency of these tumors to invade the blood stream locally; (2) the occurrence of generalized carcinomatosis by blood dissemination, and (3) the signs caused by secondary growths in two patients which obscured the clinical picture. There was definite evidence of dissemination by way of the blood stream in two cases of adenocarcinoma, and in two others there was invasion of the portal vein or its branches, in which, however, no generalized distribution of tumor foci occurred.

#### REPORT OF CASES

The following extracts from the protocols serve to illustrate the invasion of the venous system:

CASE 1.—L. K., male, aged 33. Necropsy by Dr. S. B. Wolbach. Carcinoma of head of pancreas. "On opening the portal vein it is found to be surrounded by tumor (primary) for a distance of 6 to 7 cm. At the lower margin of the tumor at the level of the entrance of the superior mesenteric vein it has a plaque-like thrombus of friable whitish material and upon removal of this thrombus the intima is found roughened, elevated and firm, and it is evident that tumor has extended into the vein at this point."

CASE 2.—O. S., male, aged 75. Necropsy by Dr. S. B. Wolbach. Carcinoma of tail of pancreas. "Dissection of the extrahepatic portion of the portal vein shows nothing unusual, but a probe introduced into the splenic vein meets resistance where it enters the tumor and here it is completely occluded. The splenic vein is picked up at the hilus of the spleen and two branches of large size are found running in the gastro-splenic omentum to the greater curvature of the stomach, while the splenic vein itself enters the tumor where it is compressed and occluded by the firm growth. Further dissection of the portal vein shows the branches going to the left lobe to be normal. The main branch going to the right lobe is completely occluded by a tumor nodule. The occluded portion is preceded by a short distance of vein which is flattened by surrounding tumor. The large branches of the hepatic vein opening into the vena cava from the right are compressed and a few small yellowish nodules from 1 to 2 mm. in diameter are present in the intima. Such vessels when followed into the

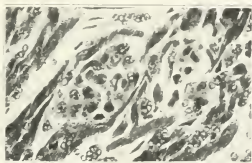


Fig. 1.—Metastatic foci in myocardium. High power.

substance of the liver appear to be occluded completely where they enter the tumor nodules." This man also showed occlusion of the hepatic duct within the liver substance.

In the patients in whom more generalized distribution occurred, invasion of larger vessels was not demonstrated but there seems little doubt that the process by which the tumor spread is similar in the two types, and that secondary growths at more distant points owe their origin to invasion of the venous system either at the seat of the primary growth or in the liver.

Of the two cases in which secondary tumors were numerous, the first showed metastases in the liver, lungs, suprarenals and brain. In the liver there were the usual large umbilicated nodules and in the suprarenals there was practically complete replacement of parenchyma by tumor growth. Both lungs presented typical small plaques on their pleural surfaces and within the substance of the organs, and in addition the left lung showed a rather unusual picture.

CASE 3.—W. D., male, aged 50. Necropsy by Dr. F. D. Adams. Carcinoma of head of pancreas. "The upper lobe of the left lung is firm, collapsed, contracted, and about one fourth of the normal size. It is drawn over toward midline and is adherent to adjacent pericardium. On tracing the upper branches of the pulmonary artery and vein and the bronchus into this lobe they are all found to be completely occluded by the firm mass of tissue. The pulmonary artery on the medial side of the obstruction contains within its lumen, posteriorly, a raised reddish mass, adherent to wall and which on section has a yellowish center, giving the appearance of tumor metastasis with superimposed thrombus. The firm upper lobe on section shows a dark greenish blue anthracotic surface with scattered areas of greenish yellow fading into surrounding tissue. Microscopic examination showed practically complete destruction of lung tissue, the architecture being in places entirely destroyed by tumor cells having a tendency toward alveolar formation, but with a dense fibrous tissue stroma. In this mass, as well as in other foci in the lung, there were found areas in which cells were smaller than the typical tumor cells and were surrounded by homogeneous, structureless material interpreted as being colloid.

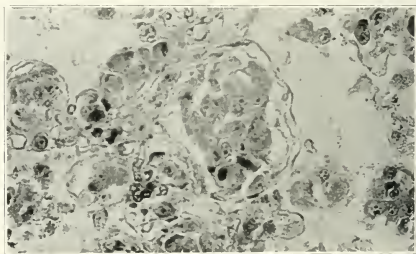


Fig. 2.—Metastatic focus in alveoli of lung. High power.

This material was also found free in irregular spaces in the stroma without relation to tumor cells which had probably been present previously but had degenerated. Other places in the lungs showed invasion by small masses of tumor tissue which followed outlines of the pulmonary alveoli, but tumor cells could not be demonstrated within the alveolar capillaries.

Foci of tumor growth were found scattered through the cortex and white matter of the brain in this patient, being described as small irregular areas of discoloration, brownish, somewhat gelatinous, irregularly outlined and poorly demarcated. They proved to be, on microscopic study, metastases involving brain tissue and in places overlying meninges as well. Here there were frequently found blood vessels filled completely or partially with clumps of tumor cells and sometimes lying a short distance apart from the tumor focus. Colloid change was prominent in all the foci examined in this brain.

Colloid was found also in one other case, but in the latter it was present in the primary growth as well as in the metastases, whereas

in the instance just discussed the tumor in the pancreas was a pure adeno-carcinoma.

The most unusual case of the series is one in which a diffuse carcinomatosis occurred with widely distributed metastases.

CASE 4.—M. Ca., female, aged 47. Necropsy by Doctor F. D. Adams.

Body: Obesity. Pallor suggesting quite severe anemia. Edema about left eye. Swelling of deeper tissues in region of angle of jaw, extending well down into the neck. Beneath, a hard irregular nodular mass is palpable, which appears to be a tumor involving the parotid gland and regional nodes as well.

Peritoneal Cavity: Numerous small white, slightly raised tumor nodules scattered at irregular points on the intestinal surfaces, averaging from 2 to 3 mm. in diameter. Mesenteric lymph nodes enlarged and show evidence of invasion.

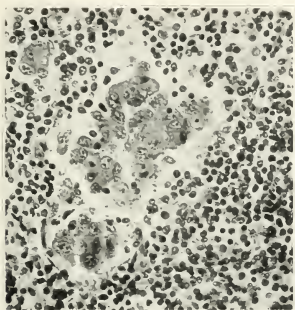


Fig. 3.—Metastatic focus in malpighian body of spleen. High power.

Pleural Cavities: Tumor nodules on diaphragmatic surface.

Mediastinum: Nodules present in the fatty tissue surrounding the pericardium and on external surface of pericardium, but none on its inner surface.

Heart: Normal size. Nodules averaging from 3 to 4 mm. in diameter on the epicardial surface. Endocardium shows a number of tumor plaques and nodules in right auricle and ventricle. Valves and myocardium not remarkable.

Lungs: Tumor nodules present on pleural surfaces and within substance of the organs.

Spleen: No gross evidence of tumor invasion.

Gastro-intestinal Tract: Nodules on peritoneal surfaces as noted. Similar nodules scattered through mucosa of stomach, small and large intestines.

Pancreas: Enlarged, firm, hard and nodular. Outer surface studded throughout with closely packed tumor nodules, raised over surface from 1 to 5 mm. Involvement of peripancreatic tissue by tumor nodules as well. On section, gland is largely replaced by tumor throughout, but small areas of normal appearance are seen lying between nodules.

Liver: A few small and large (about 1 cm. in diameter) nodules are present. Gallbladder and ducts: Not remarkable.

Kidneys: Both organs show tumor nodules in cortex and medulla, varying from 1 to 3 mm. in diameter. Passive congestion. Both pelves bright red in color, showing extreme degree of hemorrhage into mucosa.

Suprenals: Not remarkable.

Bladder: Not remarkable.

Uterus: Tumor nodules within mucosa.

Ovary: Not remarkable.

Neck: Piece of tissue removed from region of left parotid gland shows tumor infiltration.

Brain: No evidence of tumor externally or on section after fixation.

*Microscopic Examination.*—Heart: Several small nests of epithelial cells of tumor type are seen in the myocardium, particularly in capillaries and small blood vessels.

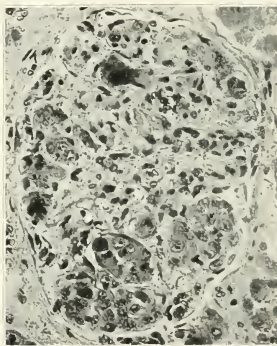


Fig. 4. Metastatic focus in glomerulus of kidney. High power.

Lungs: Alveolar capillaries show tumor emboli varying from single cells to small clumps. They are included within the capillaries but many have invaded surrounding tissue, and lie free in the alveoli. In some sections they form long cords of cells outlining alveoli. In one section there are large tumor masses, the largest measuring 4 mm. in diameter, of typical cells arranged in alveoli and cords. Mitoses are numerous. There is quite marked edema.

Spleen: Isolated small clumps of tumor cells are found in the malpighian bodies, as well as in the pulp.

Stomach: There is one section which shows high elevation of mucosa due to infiltration of submucosa and portions of mucosa by tumor cells.

Small Intestine: An occasional group of tumor cells is seen in the mucosa.

Large Intestine: Tumor cells are present singly and in small groups.

Pancreas: Two sections contain tumor nodules, some of them as wide as 3 mm. Nodules are composed of epithelial cells staining typically and arranged in alveolar form. There is attempted encapsulation with considerable interstitial pancreatitis resulting in atrophy of alveolar parenchyma. Mitotic figures are numerous.

**Liver:** In one section there is a large tumor nodule 14 mm. wide composed of alveoli of epithelial cells surrounded by a fine fibrous stroma. There is also dissemination through the liver substance, the capillaries containing tumor cells in varying numbers.

**Kidneys:** A large number of glomeruli contain a few tumor cells in the capillary tufts, in most instances the cells lying entirely within the lumina of the vessels. Larger areas of tumor invasion are also present.

**Suprarenals:** A few groups of tumor cells present in capillaries of medulla.

**Bladder:** A few tumor cells in occasional capillaries are found in the muscularis.

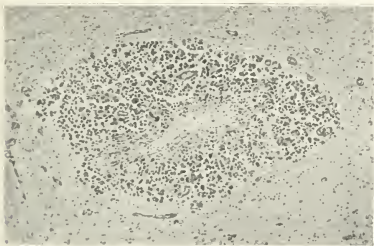
**Uterus:** Negative, except for marked obliterative endarteritis.

**Ovaries:** Numerous tumor nodules are present in vascular spaces, apparently lymphatics.

**Bone Marrow:** Tumor cells are present in large numbers.

**Mesenteric Lymph Nodes:** Show almost complete replacement by tumor growth.

**Brain:** Foci of tumor metastasis are found in the brain cortex. For the most part these foci consist of tumor cells situated in perivascular spaces, although in some parts cerebral tissue has been invaded, the center of growth being apparently a perivascular space.



(Fig. 5.—Metastatic foci in brain showing perivascular growth. Low power.)

In this group of cases the carcinoma of the pancreas showed a definite tendency to invade local blood vessels and to disseminate metastases to the liver and lungs, and in some instances to other parts of the body. The type of tumor in which this occurs is the adenocarcinoma. While the primary tumor may be essentially of adenocarcinoma type, colloid change may occur in primary or secondary growths.

It is of interest from the clinical standpoint to note that in the two cases showing the widest dissemination there were signs due to secondary invasions which were of such a nature as to obscure the diagnosis. One patient (W. D., Case 3) showed a mass of collapsed lung and tumor in the upper left chest and a lesion in this region was demonstrated on physical examination and by roentgen ray. (Pulsation of the mass was observed under the fluoroscope.) These facts,

taken into consideration with a systolic murmur at the apex and a diastolic murmur in the third interspace on the left, pupillary signs, abnormalities of the deep reflexes and a positive Wassermann reaction in the blood serum, caused several observers to record a diagnosis of syphilis, aneurysm and syphilis of the liver. There was no evidence of syphilis at the necropsy, the jaundice being due to biliary obstruction just above the ampulla, the central nervous system signs probably being due to areas of softening in the brain, and the heart murmurs possibly to pressure on the vessels by the growth in the lungs. The presence of tumor metastases in the brain, and the demonstration of tumor cells within capillaries, make it seem probable that the infarctions were due to invasion of cerebral vessels by tumor or their occlusion by tumor emboli.

PATHOLOGIC ANALYSIS OF EIGHT CASES OF MALIGNANT TUMORS OF PANCREAS

Name	Location	Liver	Regional Lymph Nodes	Lungs	Parietal Pleura	Stomach	Duodenum	Kidneys	Suprarenals	Venous Invasion	Biliary Obstruction	Type
M. R.	Head	+	+	+	+	+	+	+	+	+	+	Scirrhus
G. P.	Diffuse	+	+	+	+	+	+	+	+	+	+	Scirrhus
C. M.	Diffuse	+	+	+	+	+	+	+	+	+	+	Adenocarcinoma with colloid
M. Ch.	Head	+	+	+	+	+	+	+	+	+	+	Islands of Langerhans
L. K.	Head	+	+	+	+	+	+	+	+	Portal	+	Adenocarcinoma
O. S.	Tail	+	+	+	+	+	+	+	Left (extension)	Splenic hepatic portal Pulmonary cerebral Diffuse	Intra-hepatic	Adenocarcinoma
W. D.	Head and body	+	+	+	+	+	+	+	+	+	+	Adenocarcinoma with colloid
M. Ca.	Diffuse	+	+	+	+	+	+	+	+	+	+	Adenocarcinoma
Total.....		6	5	5	4	4	4	1	4	4	4	

In the case of M. Ca. (Case 4) there was a history of profuse bleeding per urethra for five days prior to admission to the hospital. Cystoscopic examination revealed a normal bladder and a normal urethral orifice on the right with a normally clear efflux. On the left, however, the orifice was pouty and there was no efflux during prolonged observation. The patient passed almost pure blood per urethra while in the hospital, but further study was impossible because of her poor condition. The genito-urinary findings, however, taken in conjunction with general signs of malignant disease, pointed toward a diagnosis of hypernephroma.

On microscopic examination, the most unusual feature of this case is the presence of extensive metastases within glomerular tufts. About half the number of tufts in each kidney contain groups of tumor cells.



Often one can see only two or three tumor cells plugging a capillary channel; in other cases the glomeruli are almost completely filled with them. Occasionally, tumor crescents fill and distend the capsular spaces. Mitotic figures are numerous in these secondary growths. Larger branches of the renal veins show areas of thrombosis, some fresh, others older, with beginning organization. Occlusion of these vessels does not appear to be complete. No tumor cells have been demonstrated in these thrombi. The disturbances of circulation in the kidney due to these glomerular metastases and to thrombosis probably account, in part, at least, for the extensive pelvic hemorrhages leading to hematuria.

Persistent jaundice, due to obstruction of bile ducts, is regarded as one of the most important signs of pancreatic carcinoma, and it has been estimated that it occurs in about three fourths of such cases.<sup>2</sup> In the series of eight cases under discussion, this feature was present in only four instances. There was obstruction at the ampulla in the two scirrhus cases, just above the ampulla in a third case, and of the intrahepatic portion of the hepatic duct in a fourth case. In the latter instance, occlusion was caused by a metastatic growth and not by primary tumor, which was in the tail. Four patients, in two of whom the head was involved primarily, showed no obstruction, despite the fact that in three of them there was extensive involvement of portions of the duodenum.

Clinically, carcinoma of the pancreas was strongly considered in three of the four cases with jaundice, but received practically no attention in the cases where this factor was not present. However, on reviewing the clinical records of the latter patients, after the necropsies, it was found that no features had been overlooked which should have given a key to the correct diagnosis.

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2. Osler and McCrae: *Modern Medicine*, Ed. 2, New York, Wm. Wood & Co., 1914, Vol. 3, p. 652.

## BRONCHIAL ASTHMA: RESPONSE TO PILOCARPIN AND EPINEPHRIN \*

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NEW YORK

The causes and factors apparently responsible for bronchial asthma vary widely among different individuals. One feature common to all patients with this disease is the presenting symptom—a paroxysm of difficult breathing. In studying patients during intervals of freedom from these attacks, attempts have been made to associate other conditions with bronchial asthma. It has been considered as being due to a vasomotor neurosis,<sup>1</sup> to an exudative diathesis,<sup>2</sup> to increased tone of the vagus nerve,<sup>3</sup> to sensitiveness to foreign proteins,<sup>4</sup> to a disordered metabolism,<sup>5</sup> bacterial infection of the respiratory tract,<sup>6</sup> and to certain abnormalities in the nose.<sup>7</sup>

During the past winter a series of patients with bronchial asthma was studied in detail in the hope of correlating any findings which all, or nearly all, might present. From these individuals careful histories were obtained and physical examinations were made, with special reference to lesions of the nose and throat; signs of vagotonia; status lymphaticus, roentgenograms of the chest and, when indicated, of the paranasal sinuses and the gastrointestinal tract; blood counts, sputum examinations, response to pilocarpin and epinephrin, and cutaneous reactions to foreign proteins. In the latter test only very distinct reactions were called positive. Bacterial proteins were not used because of the uncertainty of their action. Most cases showed emphysema in some degree, judged both by physical signs and roentgen-ray findings and also abnormal nasal conditions; many cases showed a steady hyper-eosinophilia in the blood and, during attacks, in the sputum; many showed a low systolic blood pressure and increased roentgen-ray lung markings. These usually consisted of increased hilus shadows from

\* From the Second Medical Division of Bellevue Hospital and the Department of Medicine, Cornell University Medical College.

1. Weber, E.: *Arch. f. Physiol.*, p. 63, 1914.

2. Von Strümpell, A.: *A Textbook of Medicine*, Ed. 4, New York, 1913, p. 220. Czerny, A.: *Jahrb. f. Kinderh.* **61**:199, 1905.

3. Eppinger, H., and Hess, L.: *Ztschr. f. klin. Med.* **67**:345, 1909; **68**:205, 1909.

4. Meltzer, S. J.: *Tr. Assn. Am. Phys.* **25**:66, 1910. Talbot, F. B.: *Boston M. & S. J.* **171**:708, 1914. Walker, I. C.: *Boston M. & S. J.* **179**:288, 1918.

5. Adam, J.: *Asthma and Its Radical Treatment*, New York, 1917.

6. Walker, I. C., and Adkinson, J.: *J. Med. Research* **40**:229, 1919. Goodale, J. L.: *Boston M. & S. J.* **174**:223, 1916.

7. Matthews, J.: *Med. Rec.* **84**:512, 1913.

which bronchial outlines spread well out into the periphery of the plate, and frequently well up into the apices. Very often the roentgenologic diagnosis of these plates was that of tuberculosis; but there was no further evidence to confirm this. The outstanding feature of these examinations was the almost constant sensitiveness to pilocarpin.

Eppinger and Hess,<sup>8</sup> as well as Barker and Sladen,<sup>9</sup> and others<sup>9</sup> have confirmed clinically the earlier pharmacologic observations of Langley, that pilocarpin stimulates some of the vagus nerve fibers, as contrasted with epinephrin, which acts on those of the true sympathetic system.<sup>10</sup> Consequently, pilocarpin evokes a response in organs innervated by certain branches of the vagus, as well as in the salivary glands,

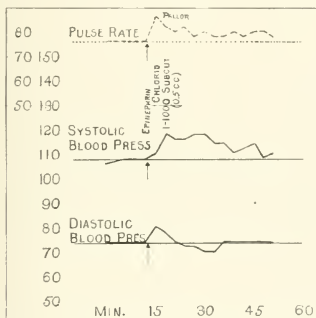


Fig. 1.—Response to epinephrin chlorid, 0.5 c.c. of 1:1,000 solution (Parke, Davis & Co.), administered subcutaneously, of an apparently normal individual.

the vasodilators of the head, and in the sweat glands, which many authors believe belong to the "extended vagus" or autonomic system.<sup>11</sup> Stimulation by adequate doses of pilocarpin, therefore, may lead to salivation, sweating, flushing, moisture of the eyes and asthma, for the circular muscles of the bronchioles are also innervated by the vagus. Eppinger and Hess maintain that bronchial asthma is an example par

8. Barker, L. F., and Sladen, F. J.: *Tr. Assn. Am. Phys.* **27**:471, 1912.

9. Petré, K., and Thorling, I.: *Ztschr. f. klin. Med.* **73**:27, 1911. Lehmann, G.: *Ztschr. f. klin. Med.* **81**:52, 1915. Bauer, J.: *Deutsch. Arch. f. klin. Med.* **107**:39, 1912.

10. Elliott, T. R.: *J. Physiol.* **32**:401, 1905.

11. Fröhlich, A., and Loewi, O.: *Arch. f. exper. Path. u. Pharmacol.* **59**:34, 1908.

excellence of heightened vagus tone, or vagotonia, but give only one case report to substantiate it. Barker and Sladen cite two cases of bronchial asthma which responded with flushing, sweating, etc. to small doses of pilocarpin and, therefore, they considered these to be vagotonics.

TABLE 1.—RESPONSE OF NORMAL INDIVIDUALS TO PILOCARPIN:  
0.003 GM. ( $\frac{1}{20}$  GRAIN) SUBCUTANEOUSLY

Number	Asthmatic Breathing	Salivation	Sweating	Epiphora	Flushing	Feeling of Warmth
1	0	0	0	0	0	0
2	0	+	0	0	0	0
3	0	0	0	0	+	+
4	0	0	0	0	0	0
5	0	0	0	0	+	0
6	0	0	+	0	0	0
7	0	0	0	0	+	+
8	0	0	+	0	0	0
9	0	0	0	0	0	0
10	0	0	+	0	0	0
11	0	0	0	0	0	0

Reactions appeared within twenty minutes.

TABLE 2.—RESPONSE OF PATIENTS WITH BRONCHIAL ASTHMA TO PILOCARPIN:  
0.003 GM. ( $\frac{1}{20}$  GRAIN) SUBCUTANEOUSLY. (TESTED DURING  
INTERVAL OF FREEDOM FROM ATTACKS)

Number	Asthmatic Breathing	Salivation	Sweating	Epiphora	Flushing	Feeling of Warmth
1	+	+	++	+	++	+
2	+	++	+	+	++	+
3	+	+	+	++	+	+
4	+	+	+	+	+	+
5	+	+	++	+	+	+
6	+	+	0	++	+	+
7	+	+	++	+	+	+
8	+	++	++	++	+	+
9	+	++	++	0	+	+
10	+	+	+	0	+	+
11	0	+	+	++	++	+
12	0	+	+	+	+	+
13	0	+	+	+	+	+
14	0	+	+	+	+	+
15	0	+	+	+	+	+
16	0	+	0	+	0	+
17	0	0	+	+	0	0
18	0	+	0	+	0	0
19	0	0	0	0	0	0
20	0	0	0	0	0	0

Reactions appeared within twenty minutes.

Most investigators recommend 0.01 gm. (about  $\frac{1}{6}$  grain of the drug) to bring out these reactions, but as this evidently gives marked response in many normal individuals, we deemed it wiser to use small doses, and in this series approximately 0.003 gm. ( $\frac{1}{20}$  grain) was employed. To this dose normal people gave very scant or no response, whereas vagotonic patients with or without asthma gave varying degrees of reaction (Tables 1 and 2).

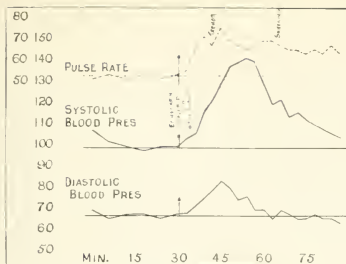


Figure 2a

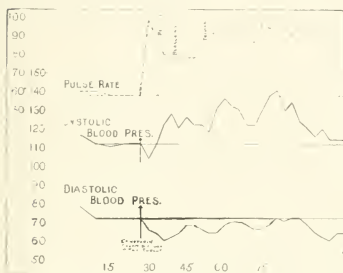


Figure 2b

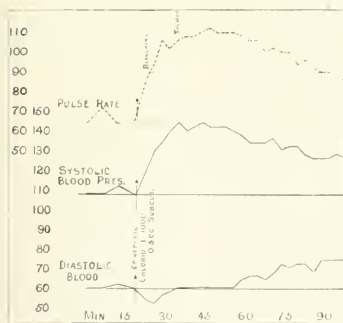


Figure 2c

Fig. 2.—Types of response to epinephrin chlorid, 0.5 c.c. of 1:1,000 solution (Parke, Davis & Co.), administered subcutaneously, in three cases of bronchial asthma with low blood pressures. Physical examination had revealed no evidences of hyperthyroidism in these cases.

It is conceded by many of the above authors that pilocarpin may not bring out all evidences of increased vagus tone. For instance, it has no constant action on the human heart rate. They have shown that negative pilocarpin reactions may not rule out vagotonia and that other signs and associated conditions must be looked for. These include eosinophilia, dermatographism, absent gag reflex, bradycardia, low blood pressure, pulsus irregularis respiratorius, and the presence of status lymphaticus. This condition, which is more easily recognized clinically in the male, occurred in eight of the fourteen men in our series. Cases were considered as being cases of status lymphaticus when they showed a transverse pubic hair line, absence of thoracic and abdominal hair, scant axillary hair, scant facial hair of typical con-

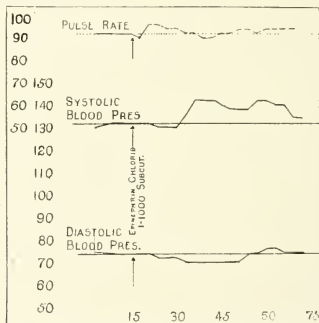


Fig. 3.—Type of response to epinephrin in a case of bronchial asthma with normal blood pressure.

figuration, smooth skin, arching thighs, and broad type of pelvis. In this series the asthmatic attacks and the incidence of all of these signs was of such frequency as to support the contention that a large proportion of these cases may belong to the clinical group which the writers mentioned above have designated as vagotonic.

It has been found by Petrén and Thorling<sup>9</sup> and others<sup>12</sup> that a small percentage of their cases responded both to pilocarpin and epinephrin. In such cases these authors therefore claim the coexistence of a heightened irritability of the autonomic and of the true sympathetic portions of the involuntary nervous system, rather than an increased

12. Wilson, R. M., and Carroll, J. H.: *The Nervous Heart*, London, 1919.

tonus of either. Apparently normal individuals, or those in whom there is adequate balance between the vagus and true sympathetic systems, rarely give such a response.<sup>13</sup> Little attention has been paid to the condition of the balance between the two factors of the involuntary nervous system in patients with bronchial asthma. Petré and Thorling,<sup>9</sup> Lehmann,<sup>9</sup> Falta, Newburgh and Nobel,<sup>14</sup> and Wearn,<sup>15</sup> each cite only one positive case of epinephrin sensitiveness in asthma, while Eppinger and Hess deny its occurrence. Figures 2 and 3 show the results of tests with epinephrin.

TABLE 3.—ANALYSIS OF THE SERIES SHOWING AN INTERESTING RELATIONSHIP BETWEEN EPINEPHRIN RESPONSE AND BLOOD PRESSURE \*

Number	Age	Pilo- carpin Reaction	Epi- nephrin Reaction	Before Epinephrin		Maximal Rise	
				Systolic Blood Pressure	Pulse	Systolic Blood Pressure	Pulse
1	59	—	—	100	72	156	72
2	61	+	—	110	80	135	116
3	53	+	—	98	52	140	75
4	44	—	—	109	60	144	95
5	34	—	+	95	70	120	81
6	26	+	+	103	81	135	110
7	35	+	0	120	75	...	...
8	51	—	0	138	57	...	...
9	25	—	0	138	61	...	...
10	52	—	0	132	92	...	...
11	51	—	0	(168)	70	...	...
12	36	—	—	120	88	142	116
13	19	—	+	100	76	126	91
14	15	+	—	105	65	144	112
15	45	+	+	100	59	140	87
16	33	+	0	95	53	...	...
17	49	+	0	120	70	...	...
18	29	+	—	109	60	138	78
19	27	0	+	102	75	129	90
20	46	0	+	110	72	134	89

\* Epinephrin response occurred only when the systolic blood pressure was low, except in Case 12, whereas, with this single exception, no reaction occurred when the blood pressure approximated the normal. One case with a low systolic blood pressure (Case 16) failed to give a positive reaction.

Janeway and Park<sup>16</sup> studied the effect of epinephrin on excised arterial strips. They found that this drug worked best on relaxed arterial walls, and least on constricted ones, which offered less range of action. Swann<sup>17</sup> made similar inferences as regards the disappearance of urticarial wheals under epinephrin, where extreme local vasodilatation offers the best opportunity for constrictor action. Park<sup>18</sup> infers a similar mechanism in bronchial asthma. The constricted bronchioles allow great excursion to the stimulus of epinephrin, which here has a dilator effect.

13. Wearn, J. T., and Sturgis, C. C.: *Arch. Int. Med.* **24**:247 (Sept.) 1919.

14. Falta, W.; Newburgh, L. H., and Nobel, E.: *Ztschr. f. klin. Med.* **72**: 97, 1911.

15. Wearn, J. T.: *Med. Rec.* **98**:164, 1920.

16. Janeway, T. C., and Park, E. A.: *J. Exper. M.* **16**:541, 1912.

17. Swann, A. W.: *Am. J. M. Sc.* **145**:373, 1913.

18. Park, E. A.: *J. Exper. M.* **16**:558, 1912.

In patients of this series with low blood pressures and bronchial asthma, obviously the two factors, bronchial constriction and peripheral vasodilatation, occur. It has been an interesting observation that in many of these cases very small amounts (0.25 c.c.) of epinephrin (1:1,000) sufficed to relieve asthmatic paroxysms, as contrasted with the asthmatic patients with normal blood pressures who gave no epinephrin response. In the latter group it required larger doses to attain the same result. Similarly, the sensitive cases reacted to the drug test where 0.5 c.c. of epinephrin chlorid, 1:1,000, was employed, with distinctly unpleasant symptoms, and often with exorbitant rises of blood pressure and pulse. These symptoms were absent in the latter group (Table 3). It is obvious that the habitually larger therapeutic dose of this powerful drug as used in bronchial asthma may be greatly in excess of requirement. This may be felt by the patient as a blow from a club, rather than the support of a crutch to his unbalanced visceral mechanism. Caution is, therefore, urged against the promiscuous use of adrenalin in asthma.

Higier<sup>19</sup> and others cite Addison's disease as the best clinical example of vagotonia due to epinephrin insufficiency. It has been shown that in this condition there may be an enormous rise in the blood pressure after epinephrin. The thought is, therefore, suggested that in subjects with bronchial asthma who are sensitive to epinephrin, the increased vagus tone and irritability may be due to a corresponding lack of tone of the opposing sympathetic system, which remains sensitive, and still able to react sharply to the stimulus, epinephrin. The association of constitutional defects such as status lymphaticus with many other functional disturbances of the viscera, and a general inability of its subjects for the high grade function demanded for great bodily exertion, give a possible clue to the nature of these defects. It is possible that a lack of balance predisposes these patients to the excessive reactions which form the presenting symptoms of bronchial asthma.

The outstanding feature of this series of cases is the frequency with which the same individual showed abnormal irritability of the two opposing divisions of the involuntary nervous system, as indicated by the response to the two test drugs. This peculiarity is not confined to bronchial asthma. Wilson and Carroll<sup>12</sup> made similar observations in cases of disordered action of the heart in soldiers, and Bauer,<sup>8</sup> Petré and Thorling,<sup>9</sup> and Lehmann<sup>9</sup> found it in functional gastric conditions and in patients usually called "neurotic."

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19. Higier, H.: *Vegetative Neurology*. Translation, Nervous and Mental Disease Monograph Series, New York and Washington, 1919.



## CONCLUSIONS

1. In a series of twenty cases of bronchial asthma, a general examination with routine laboratory aids and drug tests revealed no constant associated condition.

2. The most frequent finding was abnormally increased sensitiveness to pilocarpin. These cases frequently presented constitutional defects (status lymphaticus) and abnormal reactions described as characteristic of the condition called vagotonia.

3. The majority of cases reacted also to epinephrin with an abnormal rise in blood pressure and other characteristic signs—pallor, tremor, sometimes rigor—denoting increased sensitiveness to this drug.

4. A relation between low blood pressure and excessive epinephrin reaction was apparent, while the smaller number of cases with normal or high blood pressure gave regularly normal reactions.

5. Cases reacting excessively to epinephrin were found to be relieved by 0.25 c.c., a much smaller dose of the drug than is usually employed.

## ANGINA PECTORIS

### AN ELECTROCARDIOGRAPHIC STUDY

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Patients having angina pectoris occasionally do not present objective evidence of heart disease. This fact prompted the study reported on herewith in order to detect, if possible, alterations in the electrocardiograms of such patients.

A critical study of 155 cases of angina pectoris was undertaken, including a careful analysis of clinical histories, physical findings, electrocardiograms and other adjunct laboratory data. Nineteen patients (12.2 per cent.) had recognizable aortic lesions, four of which were of syphilitic origin. Seven patients had aortitis, four aortic regurgitation, five aortitis and aortic regurgitation, two aortic stenosis, and one patient had an aneurysm of the descending aorta. Seven patients having syphilis did not have clinical evidence of aortic disease, although the heart was invaded by disease. In this group the possibility of unrecognized aortitis producing atresia of the coronary orifices must be considered although this type of aortitis is usually recognized. Two patients (1.3 per cent.) had mitral stenosis.

The remaining 134 patients (86.5 per cent.) had indeterminate pathologic lesions, granted that we must discard the view of coronary disease accepted as true for many years and revealed at necropsy innumerable times. Allbutt's work, which appeared in 1915, was revolutionary, completely discrediting the coronary hypothesis. It is not my intention to renew the controversy which arose in this country following the publication of Allbutt's<sup>1</sup> work.

I must acknowledge that I find it difficult to classify this large group of patients (86.5 per cent.) if coronary disease is not responsible for their angina. If aortic disease was present, it was not detected clinically, and such a high percentage of diagnostic error is certainly unlikely. No instance of adhesive pericarditis was noted.

The series comprised 128 males and twenty-seven females. The greater number of patients were found in the fifth (thirty-four), sixth (fifty-nine) and seventh (forty-five) decades. Seven patients (4.6 per cent.) did not have objective evidence of heart disease and will be considered later.

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1. Allbutt, C.: *Diseases of the Arteries Including Angina Pectoris*, London, Macmillan, 1915, 2.

## ELECTROCARDIOGRAPHIC FINDINGS

Thirty electrocardiograms (19.4 per cent.), including ventricular preponderance and T wave negativity in Derivation III were considered normal. This criterion is just, I believe, since preponderance of one or the other ventricle is often observed in apparently normal hearts. Excluding the electrocardiograms having ventricular preponderance the number is twelve (7.7 per cent.).

*Changes in the Final Ventricular T Wave.*—A great deal of uncertainty has existed with regard to the mode of production of the normal T wave. Experimental and clinical studies<sup>2</sup> indicate that this wave is a contraction phenomenon resulting from changes in contraction preponderance on one side of the line of equipotential. Smith,<sup>3</sup> during his work on ligation of the coronary arteries, found that changes in the T wave were the most constant electrocardiographic findings. He found the T wave to become strongly positive first, then to become markedly negative and return more slowly to the positive or the iso-electric form.

An analysis of Smith's electrocardiograms reveals numerous instances of abrupt peaked positive T waves of exaggerated amplitude. This type of T wave is not infrequently encountered in routine clinical electrocardiography, and sharply contrasts the usual blunt curved wave of lower amplitude. It is at times present in a single derivation, but more often in combined derivations. This finding occurred in eighteen (11.6 per cent.) of the electrocardiograms in this series. Such a T wave, I believe, is evidence of rather sudden changes in contraction preponderance, indicative, probably, of increased contraction of certain muscular areas. Figures 1 and 2 illustrate the type of T wave under discussion contrasted with the normal type.

Pardee<sup>4</sup> recently published remarkable electrocardiograms of a patient with sudden coronary obstruction. A most unusual positive (upright) T wave was present, markedly exaggerated in amplitude, having a distinct moundlike contour, occurring before the completion of the R wave, and occupying 0.40 second. It was present in Derivations II and III. As improvement in the patient's condition occurred, the wave approached normal but became negative (inverted) in both derivations, especially peaked in Derivation III.

2. Eyster, J. A. E., and Meek, W. J.: The Interpretation of the Normal Electrocardiogram. A Critical and Experimental Study, *Arch. Int. Med.* **11**: 204 (Feb.) 1913. Hoffmann, A.: Zur Deutung des Elektrokardiogramms, *Arch. f. d. ges. Physiol.* **133**:552, 1910.

3. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, *Arch. Int. Med.* **22**:8 (July) 1918.

4. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch. Int. Med.* **26**:244 (Aug.) 1920.

There was no instance of acute coronary obstruction in this series. Four patients were examined soon after the onset of anginal attacks, one patient ten days after, one patient two and a half weeks after, and two patients three weeks after, but the histories and findings did not suggest sudden coronary obstruction. No outstanding electrocardiographic findings were apparent.

T wave negativity (inversion) occurring in isolated and combined derivations was present in eighty (51.6 per cent.) of the electrocardiograms. T wave negativity results from alteration in potential distribution from changes in contraction preponderance.<sup>5</sup> Changes in contraction preponderance may result from changes in blood volume, and from organic or functional myocardial fatigue. The significance of T wave negativity, in the previously reported series, as evidence of heart disease in order of gravity was (1) combined Derivations I and II, (2) Derivation I, (3) combined Derivations I, II, and III, (4) combined Derivations II and III, and (5) Derivation III. No significance can be attached to T wave negativity in Derivation III alone as it occurs in normal and in diseased hearts. Excluding T wave negativity in Derivation III, the number of patients with significant T wave negativity was fifty-one (32.9 per cent.). Table 1 records these findings in patients with angina pectoris.

TABLE 1.—T-WAVE NEGATIVITY

Decade	Total Number of Cases	Derivation I	Derivation III	Combined Derivations I and II	Combined Derivations II and III	Combined Derivations I, II and III
31-40	8	1	2	1	0	0
41-50	34	3	9	0	4	1
51-60	59	10	8	6	4	2
61-70	45	10	10	1	4	2
71-80	8	1	1	0	0	0
81-90	1	0	0	0	0	0
Total	155	25	30	8	12	5

T wave negativity in Derivation I occurred in twenty-five (16.1 per cent.) electrocardiograms, combined Derivations II and III in twelve (8.8 per cent.), combined Derivations I and II in eight (5.2 per cent.) and combined Derivations I, II and III in five (3.2 per cent.). The significance of these four types of T wave negativity is appreciated when the cardiac mortality statistics are analyzed. Thirty-seven of these patients have been heard from and twenty-six (70.3 per cent.) have died from heart disease during a period of five years. Six patients are known to have died in anginal attacks. The mortality

5. Willius, F. A.: Clinical Observations on Negativity of the Final Ventricular T Wave of the Human Electrocardiogram. *Am. J. M. Sc.* **160**:844, 1920.

in the individual groups was: (1) Derivation I, 72.0 per cent., (2) combined Derivations II and III, 66.6 per cent., (3) combined Derivations I and II, 75.0 per cent., and combined Derivations I, II and III, 80.0 per cent.

Figures 3 and 4 illustrate two sharply contrasted types of negative T wave, the rounded wave of low amplitude indicating a negativity which has existed probably for a long time, and the other, of greater amplitude and peaked, is a more recent abnormality. The latter wave is similar to those in Smith's electrocardiograms.

*Abnormal QRS Complexes in All Derivations.*—Much interest has been displayed the last few years in changes affecting the QRS complex of the electrocardiogram. Lewis<sup>6</sup> ascribed the anomalies to impairment of intraventricular conduction. In 1915 Oppenheimer and Rothschild<sup>7</sup> named the condition arborization block, and believed that lesions involving the Purkinje plexus were responsible for the bizarre complexes. Robinson,<sup>8</sup> a year later, reported similar findings, resulting, he believed, from functional myocardial fatigue. Carter<sup>9</sup> discussed the subject in two publications, calling attention to faulty conduction in the branches of the auriculoventricular bundle and to sclerosis affecting the bundle branches and arborizations. In my publication<sup>10</sup> of 1919 I expressed the belief that a structural basis is responsible for the bizarre QRS complexes, and that the arborization hypothesis seems tenable. It is my intention particularly to identify these electrocardiographic phenomena with a definite clinical picture and to emphasize the gravity of the disorder. Recent experimental work by Smith<sup>11</sup> failed to confirm the arborization hypothesis. Following coronary ligation, extensive subendocardial lesions were produced without the development of QRS changes. Abnormal complexes were, however, obtained by dividing the bundle branches and the complexes became definitely bizarre when ventricular dilatation supervened. Smith concluded that two factors were necessary for the production

6. Lewis, T.: *Clinical Electrocardiography*, London, Shaw, 1913.

7. Oppenheimer, B. S., and Rothschild, M. A.: *Electrocardiographic Changes Associated with Myocardial Involvement*, J. A. M. A. **69**:429 (Aug. 11) 1917.

8. Robinson, G. C.: *The Significance of Abnormalities in the Form of the Electrocardiogram*, Arch. Int. Med. **24**:422 (Oct.) 1919. *The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart*, Arch. Int. Med. **18**:830 (Dec.) 1916.

9. Carter, E. P.: *Clinical Observations on Defective Conduction in the Branches of the Auriculoventricular Bundle. A Report of Twenty-Two Cases in Which Aberrant Beats Were Obtained*, Arch. Int. Med. **13**:803 (June) 1914. *Further Observations on the Aberrant Electrocardiogram Associated with Sclerosis of the Atrioventricular Bundle Branches and Their Terminal Arborizations*, Arch. Int. Med. **12**:331 (Sept.) 1918.

10. Willius, F. A.: *Arborization Block*, Arch. Int. Med. **23**:431 (April) 1919.

11. Smith, F. M.: *Experimental Observations on the Atypical QRS Waves of the Electrocardiogram of the Dog*, Arch. Int. Med. **26**:205 (Aug.) 1920.

of the abnormal electrocardiogram: (1) lesions of the conduction system, and (2) cardiac fatigue. Wilson and Herrmann,<sup>12</sup> in a recent publication, state that complete bundle branch block is capable of producing characteristic Q R S changes but they do not believe that lesions of the bundle subdivisions are capable of producing such changes.

Notwithstanding the variance of views as to the mode of production of the abnormal Q R S complexes, these electrocardiograms, when all derivations are involved, are indisputably linked with a clear-cut clinical picture. Patients having this disorder have marked myocardial disintegration and the high and early mortality of this group indicates a lesion having the tendency to progress.

Clinical and experimental evidence indicates intrinsic vascular degeneration of the obliterative type as the primary cause. The progressive tendency of the lesion and its frequent association with significant T wave negativity favors this conception.

The changes constituting an abnormal Q R S complex are (1) a base width exceeding 0.10 second in complexes of unaltered contour, and (2) in aberrant complexes, notching, or splintering of the ascending or descending limb or of the apex R.

Bousfield<sup>13</sup> obtained electrocardiograms of a patient during a paroxysm of angina pectoris and the Q R S complexes in all derivations were bizarre. The base width was 0.16 second and definite notching was present. The complexes assumed normal characteristics after the paroxysm had subsided. Interesting changes in the T wave also were noted. During the attack the T wave in Derivation I was negative, which became positive later while the T waves of Derivations II and III became negative.

In this series, twenty-two (14.2 per cent.) patients had aberrant Q R S complexes in all derivations of their electrocardiograms. Sixteen of these records were associated with significant T wave negativity. T wave negativity in Derivation I alone occurred with greatest frequency, being present in eight (36.4 per cent.) of these electrocardiograms.

A high mortality occurs likewise in this group. Information regarding sixteen patients has been received; ten (62.5 per cent.) have died from heart disease and four of these died in anginal attacks.

*Abnormal Q R S Complexes in Isolated Derivations.*—Notching or slurring of the Q R S complex in isolated derivations of the electrocardiogram is less conclusive than the same changes affecting all derivations. These findings are, at times, inconstant but have been repeat-

12. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, *Arch. Int. Med.* **26**:153 (Aug.) 1920.

13. Bousfield, G.: Angina Pectoris: Changes in Electrocardiogram During Paroxysm, *Lancet* **2**:457, 1918.

edly observed over a number of years; they become more marked with the lapse of time.

Wedd<sup>14</sup> discussed these changes showing the association with definite myocardial disease in some cases. In my analysis<sup>15</sup> of 747 cases, I found the mortality attending this disorder to be 23.7 per cent. in the complete group, 11.2 per cent. higher than the control series of similar heart cases without localized notching or slurring of the Q R S complexes.

Thirty-three (21.2 per cent.) patients had notched Q R S complexes in isolated derivations of their electrocardiograms. The greatest number occurred in Derivation III, nineteen (57.5 per cent.). In order of frequency the other derivations were involved as follows: Derivation II, nine (27.9 per cent.), combined Derivations II and III, four (12.1 per cent.), and Derivation I, one (3.0 per cent.). Five (15.1 per cent.) of these electrocardiograms were associated with significant T wave negativity. Excluding these cases the cardiac mortality in the group was 47.3 per cent.

Twenty-six (16.7 per cent.) patients had slurred Q R S complexes. In ten (38.4 per cent.) patients these findings occurred in Derivation II, in eight (30.7 per cent.) in Derivation I, in seven (26.9 per cent.) in Derivation III, and in one (3.8 per cent.) in combined Derivations I and II. Eleven (42.3 per cent.) of these electrocardiograms were associated with significant T wave negativity. Excluding the cases with significant T wave negativity the cardiac mortality was 20.0 per cent.

*Delayed Auriculoventricular Conduction.*—Prolongation of the P-R interval beyond 0.22 second is abnormal and indicates delay in impulse transmission between auricles and ventricles. Only two (1.3 per cent.) patients had this abnormality in their electrocardiograms. In both cases the P-R interval was 0.24 second. In one electrocardiogram negativity of the T wave in Derivation I occurred. Information was obtained regarding one of these patients who died in an anginal attack four years after examination.

*Complete Auriculoventricular Dissociation (Complete Heart Block).*—Only one patient (0.6 per cent.) had complete auriculoventricular dissociation. The auricular rate was 94 and the ventricular rate 47 each minute. This patient died of heart disease seven and one half months after examination.

*Auricular Fibrillation.*—Three (1.9 per cent.) patients had auricular fibrillation. The infrequency of auricular fibrillation with angina pectoris is apparent and due undoubtedly to the fact that the ventricles

14. Wedd, A. M.: The Clinical Significance of Slight Notching of the R-Wave of the Electrocardiogram, *Arch. Int. Med.* **23**:515 (April) 1919.

15. Willius, F. A.: Observations on Changes in Form of the Initial Ventricular Complex in Isolated Derivations of the Human Electrocardiogram, *Arch. Int. Med.* **25**:550 (May) 1920.

bear the brunt of the ravages of the disease. Information regarding two of these patients has been received; both have died from heart disease, one two weeks and the other one year after examination.

*Ventricular Preponderance.*—Preponderance of the left ventricle occurred most frequently in 115 (74.2 per cent.) of the electrocardiograms. Preponderance of the right ventricle was present in only ten (6.4 per cent.) and no unbalance occurred in thirty (19.4 per cent.) of the tracings.

*Patients with Angina Pectoris with No Objective Evidence of Heart Disease.*—Seven patients in this series had no objective evidence of heart disease. There was nothing outstanding in their electrocardiograms. Two electrocardiograms revealed only ventricular preponderance, one was normal, except for the presence of an exaggerated P wave in Derivations II and III; three revealed notched QRS complexes in isolated derivations, and one showed T wave negativity in Derivation III. It is evident that demonstrable cardiac disease must necessarily be present to produce significant electrocardiographic abnormalities.

*Cardiac Mortality.*—The cardiac mortality of the complete group was 46.7 per cent. It is interesting to contrast this percentage with the mortality attending significant T wave negativity (70.3 per cent.) and abnormal QRS complexes in all derivations (62.5 per cent.). Sixteen patients are known to have died in anginal attacks; the information regarding the others was not specific in this regard. There was no constant relationship between the duration of angina and the degree of electrocardiographic abnormality. Figures 5 to 52 are the electrocardiograms of the fatal cases. One tracing was lost and another was indistinct, rendering reproduction impossible.

#### CONCLUSIONS

1. There are no electrocardiographic findings pathognomonic of angina pectoris.
2. Significant T wave negativity occurred in one third of the electrocardiograms (32.9 per cent.) and is an important abnormality.
3. Abnormalities in T wave contour affecting both the positive and the negative wave are significant.
4. Abnormal QRS complexes in all derivations of the electrocardiogram occurred in 14.2 per cent. of the records.
5. The cardiac mortality of the complete group was 46.7 per cent., definitely contrasted by the higher mortality attending those patients having significant T wave negativity (70.3 per cent.) and abnormal QRS complexes in all derivations (62.5 per cent.) of their electrocardiograms.



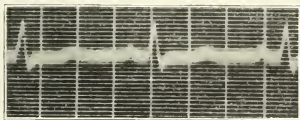


Fig. 1.—Usual type of T wave. Rounded, low amplitude wave.

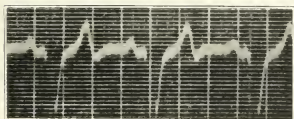


Fig. 2.—Abnormal T wave. Abruptly peaked, high amplitude wave.

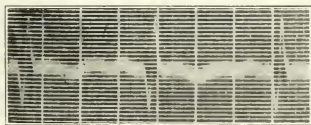


Fig. 3.—Rounded low amplitude negative T wave.



Fig. 4.—Abruptly peaked, high amplitude negative T wave.

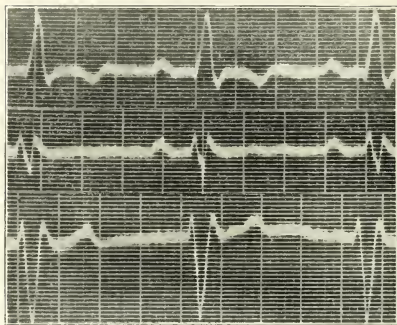


Fig. 5.—Case 160997. Angina pectoris two years. Patient died in anginal attack two weeks after examination.

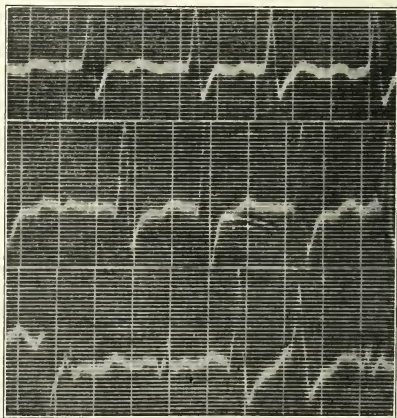


Fig. 6.—Case 170503. Angina pectoris six months. Patient died of heart disease two weeks after examination.

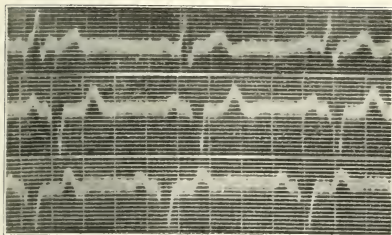


Fig. 7.—Case 206305. Angina pectoris one year. Patient died in anginal attack two weeks after examination.

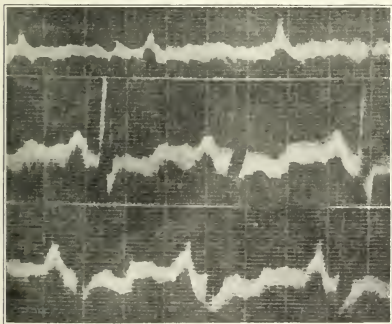


Fig. 8.—Case 150610. Angina pectoris seven months. Patient died of heart disease one month after examination.

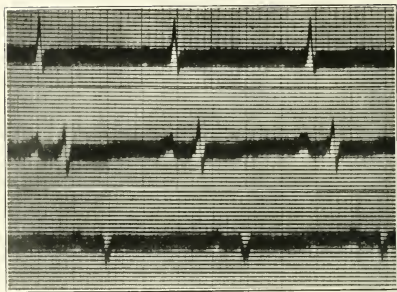


Fig. 9.—Case 126195. Angina pectoris six years. Patient died in anginal attack two months after examination.

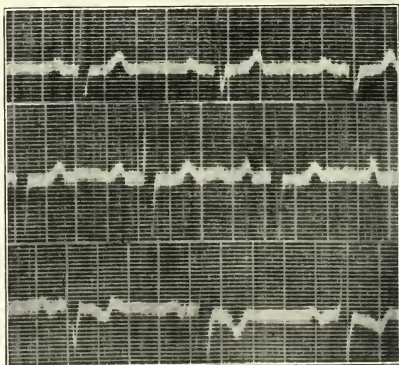


Fig. 10.—Case 242121. Angina pectoris one and one-half years. Patient died in anginal attack two and one-half months after examination.

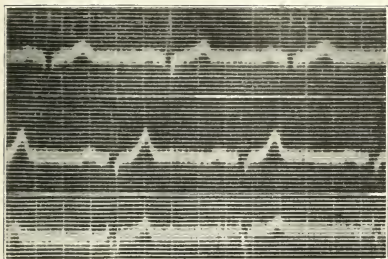


Fig. 11.—Case 203754. Angina pectoris two months. Patient died of heart disease two and one-half months after examination.

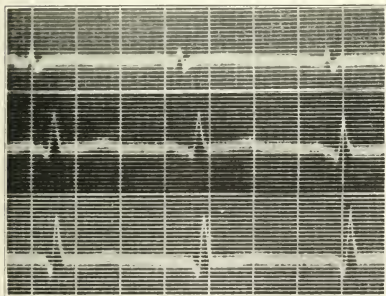


Fig. 12.—Case 167472. Angina pectoris nine months. Patient died three months after examination (aortic aneurysm).

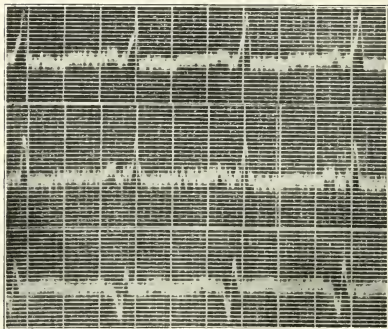


Fig. 13.—Case 179117. Angina pectoris two years. Patient died in anginal attack three months after examination.

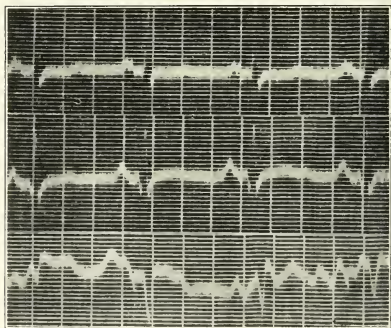


Fig. 14.—Case 222291. Angina pectoris two and one-half months. Patient died in anginal attack three months after examination.

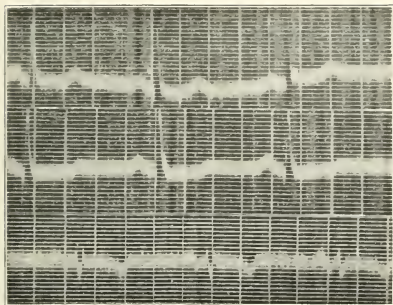


Fig. 15.—Case 248433. Angina pectoris seven months. Patient died in anginal attack three months after examination.

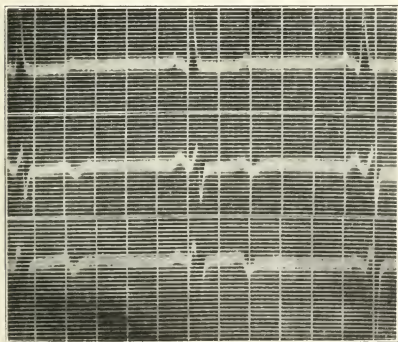


Fig. 16.—Case 221475. Duration of angina pectoris unknown. Patient died of heart disease three and one-half months after examination.



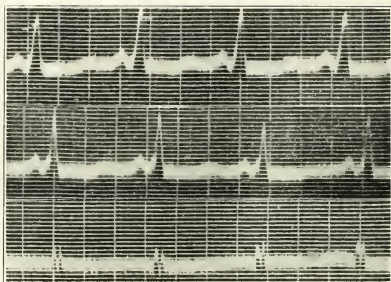


Fig. 17.—Case 206571. Angina pectoris four years. Patient died of heart disease four months after examination.

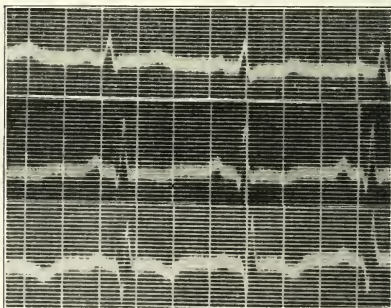


Fig. 18.—Case 218457. Angina pectoris two and one-half years. Patient died in anginal attack four months after examination.



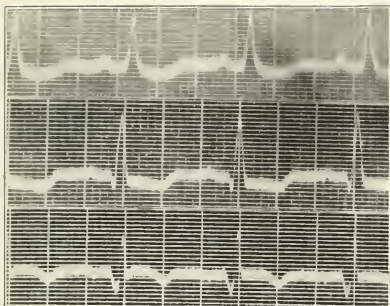


Fig. 19.—Case 157589. Angina pectoris three years. Patient died of heart disease four and one-half months after examination.

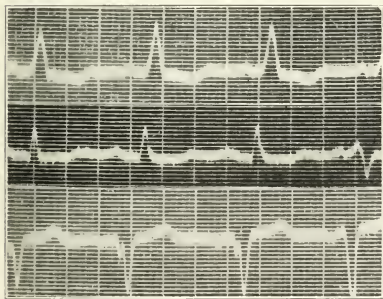


Fig. 20.—Case 173245. Angina pectoris eight years. Patient died of heart disease five months after examination.

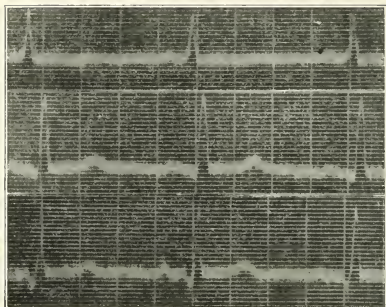


Fig. 21.—Case 153636. Angina pectoris two years. Patient died in anginal attack five months after examination.

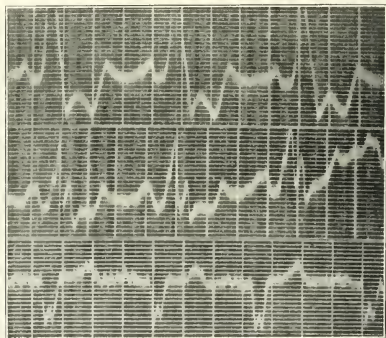


Fig. 22.—Case 236223. Angina pectoris seven months. Patient died of heart disease six months after examination.

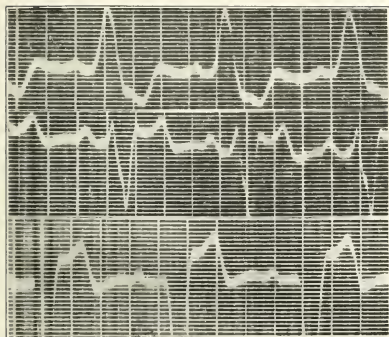


Fig. 23.—Case 236217. Duration of angina pectoris not known. Patient died of heart disease six and one-half months after examination.

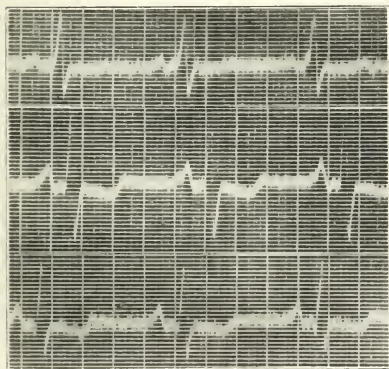


Fig. 24.—Case 176195. Angina pectoris five months. Patient died of heart disease seven months after examination.

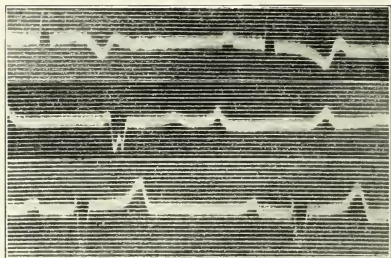


Fig. 25.—Case 198206. Angina pectoris three years. Patient died of heart disease seven and one-half months after examination.

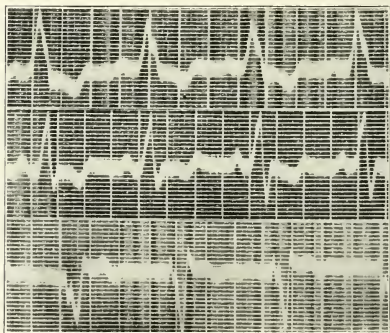


Fig. 26.—Case 245363. Angina pectoris ten months. Patient died in anginal attack nine months after examination.

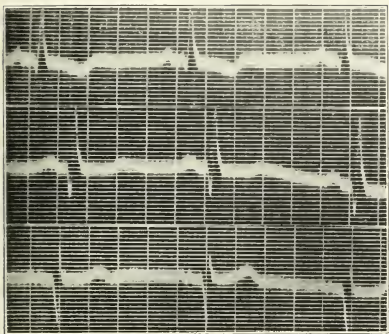


Fig. 27.—Case 96359. Angina pectoris fifteen years. Patient died of heart disease eleven months after examination.

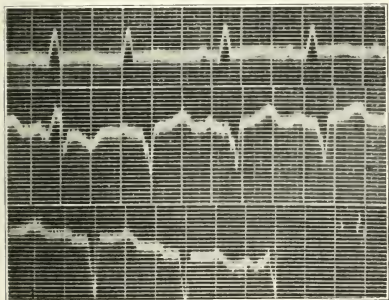


Fig. 28.—Case 180298. Angina pectoris five months. Patient died in anginal attack eleven months after examination.

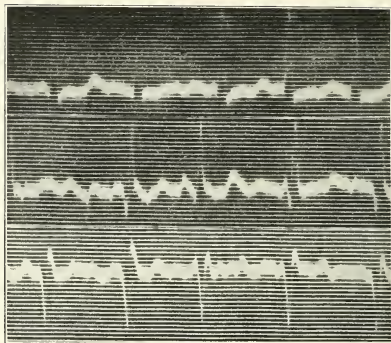


Fig. 29.—Case 201583. Angina pectoris three weeks. Patient died of heart disease one year after examination.

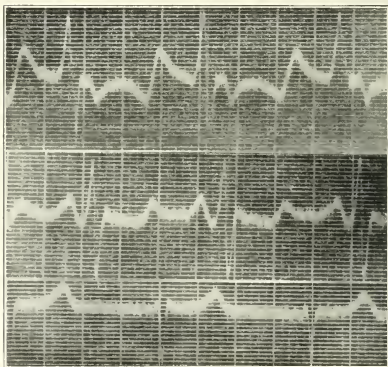


Fig. 30.—Case 160782. Angina pectoris one year. Patient died of heart disease one year after examination.

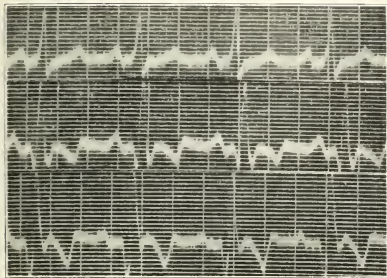


Fig. 31.—Case 178742. Angina pectoris three weeks. Patient died of heart disease thirteen months after examination.

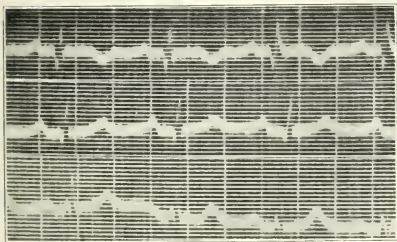


Fig. 32.—Case 147150. Angina pectoris six weeks. Patient died of heart disease fourteen months after examination.



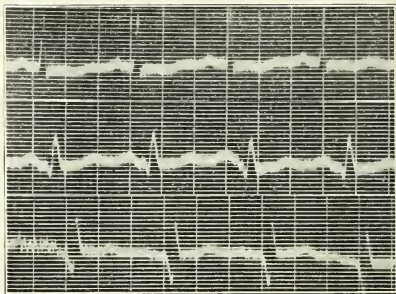


Fig. 33.—Case 97322. Angina pectoris two years. Patient died in anginal attack fifteen months after examination.

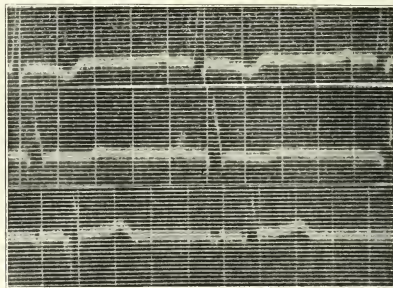


Fig. 34.—Case 145557. Angina pectoris five years. Patient died of heart disease sixteen months after examination.



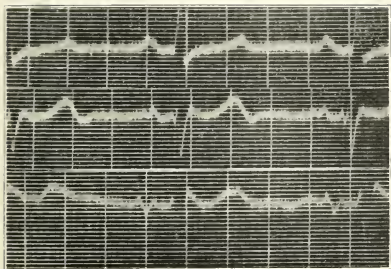


Fig. 35.—Case 158332. Angina pectoris five years. Patient died of heart disease two years and four months after examination.

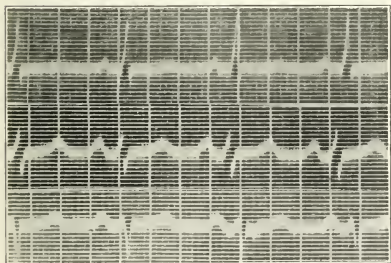


Fig. 36.—Case 226409. Angina pectoris eight months. Patient died in anginal attack twenty months after examination.

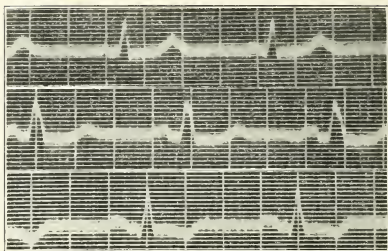


Fig. 37.—Case 153850. Angina pectoris twenty years. Patient died of heart disease twenty months after examination.

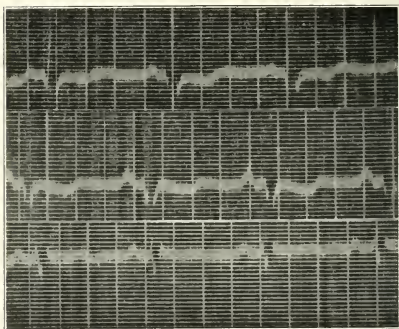


Fig. 38.—Case 242391. Angina pectoris five years. Patient died of heart disease twenty months after examination.

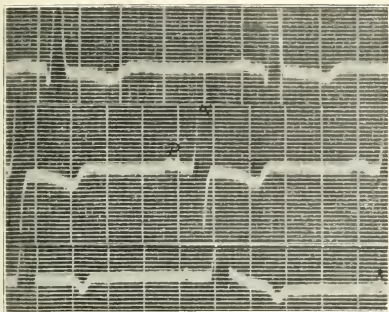


Fig. 39.—Case 136009. Angina pectoris four years. Patient died in anginal attack twenty-one months after examination.

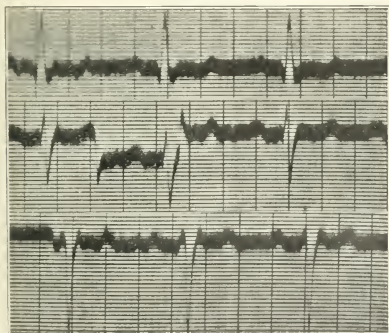


Fig. 40.—Case 129182. Angina pectoris five years. Patient died of heart disease two years after examination.

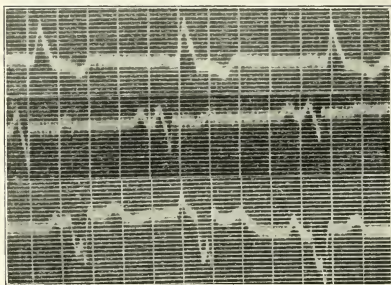


Fig. 41.—Case 228723. Angina pectoris one and one-half years. Patient died of heart disease two years after examination.

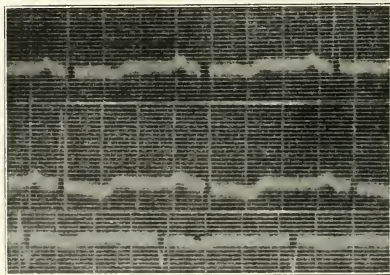


Fig. 42.—Case 148902. Angina pectoris one year. Patient died of heart disease three years after examination.

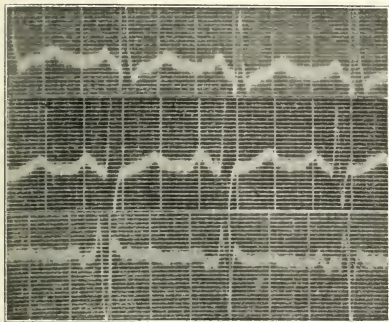


Fig. 43.—Case 142922. Duration of angina pectoris not known. Patient died of heart disease three years and two months after examination.

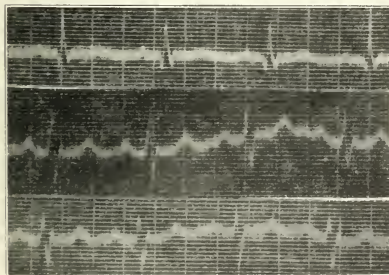


Fig. 44.—Case 176237. Angina pectoris two years. Patient died in anginal attack three and one-half years after examination.

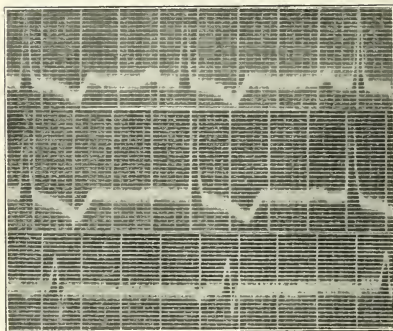


Fig. 45.—Case 142863. Angina pectoris ten years. Patient died of heart disease three years and eight months after examination.

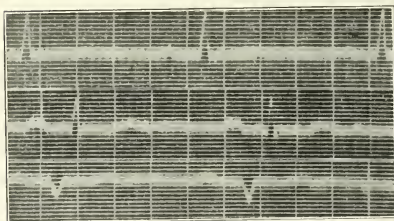


Fig. 46.—Case 145892. Angina pectoris three years. Patient died in anginal attack four years after examination.

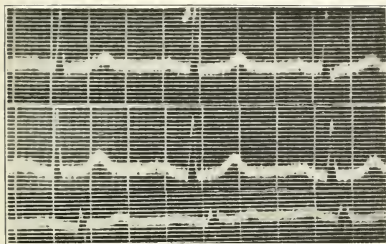


Fig. 47.—Case 144362. Angina pectoris six weeks. Patient died of heart disease four and one-half years after examination.

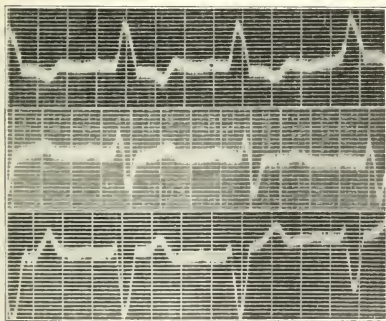


Fig. 48.—Case 180323. Angina pectoris two years. Patient died of heart disease. Date not known.



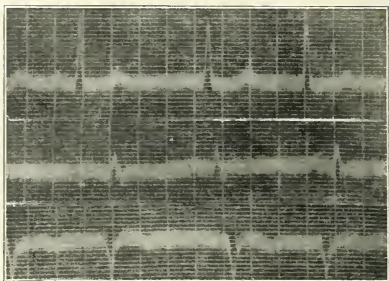


Fig. 49.—Case 247209. Angina pectoris one year. Patient died of heart disease. Date not known.

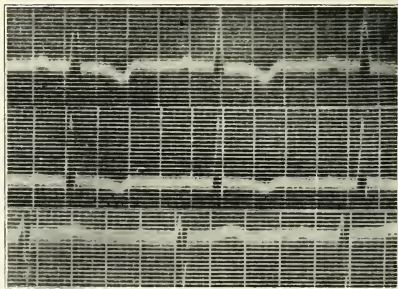


Fig. 50.—Case 164904. Angina pectoris six months. Patient died of heart disease. Date not known.



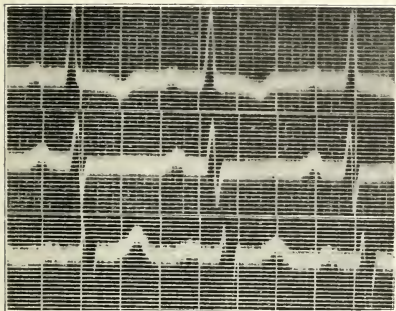


Fig. 51.—Case 160498. Angina pectoris six months. Patient died of heart disease. Date not known.

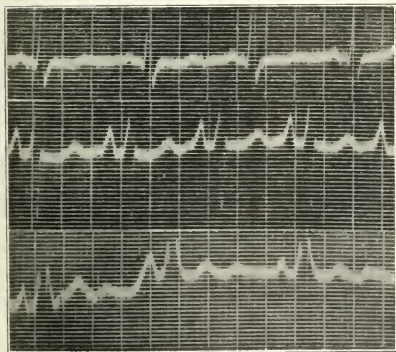


Fig. 52.—Case 182470. Angina pectoris four years. Patient died of heart disease. Date not known.

# STUDIES ON RENAL THRESHOLD FOR GLUCOSE\*

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## INTRODUCTION

The bibliography of renal glycosuria is already given by one of us.<sup>1</sup> In renal glycosuria glucose is excreted in the urine, owing to the descending of the renal threshold, while the carbohydrate metabolism is normal. The renal threshold for glucose is the smallest limit of the content of glucose in the blood, in which sugar is first to be excreted in urine.

In diagnosing renal glycosuria, it is essential to determine the content of sugar in the blood and the renal threshold for glucose. We first measured the sugar in the blood of the normal Japanese and then the alimantal hyperglycemia in the blood which occurred after giving 100 gm. glucose. In this experiment we discriminated between those who eliminated sugar in the urine after the intake and those who did not. Then, giving again a smaller quantity of glucose to those who excreted sugar, we tried to investigate the renal threshold for glucose. Finally, we made various tests of renal function in the cases of lowered threshold to see whether the renal function was normal or not. We made tests on fifty-three adults.

## I. SUGAR IN THE BLOOD OF NORMAL JAPANESE

We applied the Meyers-Bailey<sup>2</sup> method to measure the amount of sugar in the blood. For measuring the sugar in the urine, we used qualitatively the Benedict<sup>3</sup> method and the Almen-Nylander method, and quantitatively the Benedict and Osterberg<sup>4</sup> method.

1. *Sugar in the Blood of Normal Adults After a Fast Overnight.*—It is well known that sugar in the blood is increased in the normal person by the influence of food, and that it is almost constant in the morning after the fast over night. In our research the subject was not permitted to take anything after supper. He was bled at 8 a. m. and the sugar in the blood was measured. We used the plasma. The results are shown in Tables 1 and 2. The minimum was 0.066 per cent. and the maximum 0.116 per cent., the average being 0.092 per cent.

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\* From the Hospital of the Medical School, Tokyo Imperial University.

1. Goto, K.: Arch. Int. Med. **22**:96 (July) 1918.

2. Meyers, V. C., and Bailey, C. V.: J. Biol. Chem. **24**:147, 1916.

3. Benedict, S. R.: J. A. M. A. **57**:1193 (Oct.) 1911.

4. Benedict, S. R., and Osterberg, E.: J. Biol. Chem. **34**:195, 1918.

TABLE 1.—I. ALIMENTARY GLUCOSE TEST IN NORMAL PERSON. CASES WHICH EXCRETED NO SUGAR

No.	Name	Age	Glucose per Kilo Body Weight, Gm.	Urine Volume, C.c.						Blood Sugar per 100 C.c. Plasma, Gm.								Remarks	
				20 Min.	40 Min.	60 Min.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	Total Volume	Before Test	20 Min.	40 Min.	60 Min.	1½ Hr.	2 Hr.		2½ Hr.
1	A. K.	27	...	...	30	12	13	36	45	92	125	0.071	0.122	0.108	0.133	0.077	0.091	0.133	No diuresis
2	A. H.	23	...	...	17	13	18	16	16	17	97	0.070	0.118	0.101	0.110	0.084	0.081	0.118	
3	C. H.	17	...	...	14	71	71	17	11	10	213	0.080	0.115	0.057	0.088	0.087	0.072	0.050	
4	E. S.	45	...	...	22	7	10	13	11	10	83	0.080	0.102	0.160	0.146	0.136	0.123	0.094	
5	G. C.	40	...	...	20	19	28	27	32	20	179	0.083	0.136	0.100	0.127	0.098	0.075	0.136	
6	O. G.	25	...	...	21	25	40	18	17	121	160	0.080	0.174	.....	.....	.....	0.059	.....	
7	F. H.	26	...	...	16	16	20	35	18	95	...	0.090	0.151	0.141	0.105	0.097	0.042	0.163	
8	K. K.	22	...	...	53	50	17	26	25	20	...	0.109	0.134	0.172	0.170	0.123	0.087	0.172	
9	N. H.	43	...	...	30	15	14	16	18	28	150	0.109	0.153	0.112	0.112	0.144	0.131	0.153	
10	F. S.	29	...	...	18	15	7	16	12	19	101	0.116	0.176	0.183	0.174	0.170	0.135	0.185	
	Average	..	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.0896	.....	.....	.....	.....	.....	0.148	
11	L. S.	17	10.7	20	26	51	60	23	18	32	230	0.084	0.097	0.116	0.084	0.078	0.102	0.152	Diuresis
12	S. F.	34	.....	53	21	24	33	35	35	50	251	0.091	0.109	0.092	0.093	0.086	0.114	0.114	
13	F. T.	22	.....	30	19	33	66	11	74	26	259	0.101	0.131	0.101	0.081	0.069	0.073	0.131	
	Average	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.092	.....	.....	.....	.....	.....	0.132	
14	N. S.	20	.....	32	41	87	83	40	49	18	350	0.074	0.114	0.125	0.117	0.108	0.067	0.125	
15	Y. T.	21	.....	68	58	125	100	125	180	36	47	0.085	0.121	0.130	0.087	0.098	0.108	0.139	
16	F. M.	39	.....	67	79	98	100	95	200	67	594	0.085	0.104	0.088	0.091	0.087	0.079	0.148	
17	J. L.	39	.....	16	12	47	60	54	46	64	329	0.080	0.138	0.139	0.101	0.103	0.089	0.147	
18	M. K.	30	.....	26	23	18	95	34	38	39	320	0.080	0.116	0.107	0.098	0.089	0.087	0.157	
19	Y. Y.	20	.....	23	20	18	40	24	50	41	320	0.080	0.136	0.117	0.106	0.108	0.087	0.117	
20	Y. S.	21	.....	73	24	34	39	76	51	68	369	0.101	0.132	0.087	0.075	0.094	0.077	0.152	
	Average Total average	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.087	.....	.....	.....	.....	.....	0.138	
		.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	0.089	.....	.....	.....	.....	.....	0.142	



Table 3 shows that in the majority of cases the sugar content of the blood is between 0.08 and 0.11 per cent. Table four shows the sugar content of the blood of normal adults after fasting as determined by various authors.

TABLE 3.

Sugar in Blood (Plasma)	Number of Cases
0.06 - 0.07 per cent.	2
0.071 - 0.08 per cent.	6
0.081 - 0.09 per cent.	16
0.091 - 0.10 per cent.	14
0.101 - 0.11 per cent.	12
0.111 - 0.12 per cent.	2
0.121 - 0.13 per cent.	1

TABLE 4.—AMOUNT OF BLOOD SUGAR FOUND BY VARIOUS AUTHORS

Author	Method	Blood Sugar, per Cent.	Average
Naunyn.....	Abeles.....	0.07 - 0.1	
Bang.....	Bang.....	0.1 - 0.11	
Frank.....	Bertrand.....	0.06 - 0.12	
Kowarsky.....	Kowarsky.....	0.05 - 0.11	
Hopkins.....	Bang.....	0.065 - 0.11	0.085
Gettler and Baker.....	Lewis and Benedict.....	0.05 - 0.11	
Cummings and Pines.....	Cummings and Pines' modification of Lewis and Benedict's method	0.044 - 0.12	0.07
Meyers and Bailey.....	Meyers and Bailey's modification of Lewis and Benedict's method	0.09 - 0.11	
Joslin.....	Lewis and Benedict.....	0.06 - 0.11	0.10
Denis, Aub and Minot.....	Meyers and Bailey.....	0.085 - 0.12	
Goto and Kuno.....	Meyers and Bailey.....	0.066 - 0.116	0.091

## (2) Alimentary Glycosuria and Hyperglycemia in Normal Persons.

—When 100 gm. of glucose are taken in the morning, the sugar in the blood rises and reaches its maximum in from twenty minutes to one hour. It remains for two or three hours and then falls to normal or below it. The maximum is usually between 0.17 and 0.18 per cent. of sugar.

The duration of the hyperglycemia and its height are closely related to the condition of the carbohydrate metabolism of the subject, and, therefore, these factors are important in the diagnosis of diabetes. If carbohydrate metabolism is abnormal, its maximum degree is higher and the duration is longer than normal. The studies of Hopkins,<sup>5</sup> Epstein,<sup>6</sup> Hamman-Hirschman,<sup>7</sup> Cummings-Pines,<sup>8</sup> Bailey,<sup>9</sup> Williams and Humphreys<sup>10</sup> concerning the alimentary hyperglycemia of dia-

5. Hopkins, A. R.: *Am. J. M. Sc.* **149**:254, 1915.

8. Cummings, R., and Pines, G.: *Arch. Int. Med.* **19**:777 (May) 1917.

6. Epstein, A. A.: *Studies on hyperglycemia in relation to glycosuria*, 1916, New York.

7. Hamman, L., and Hirschman, I. I.: *Arch. Int. Med.* **20**:761 (Nov.) 1917.

9. Bailey, C. V.: *Arch. Int. Med.* **23**:455 (April) 1919.

10. Williams, J. R., and Humphreys, E. M.: *Arch. Int. Med.* **23**:537 (April) 1919.

betes after the glucose intake show similar results. One hundred gm. of glucose were given to three mild diabetics by Hamman and Hirschman.<sup>7</sup> The percentage of sugar rose to above 0.2 per cent. and the ascending curves were very slow, covering three or four hours. In Williams and Humphreys<sup>10</sup> report, 100 gm. glucose were given to twelve mild diabetics; only one of them showed from 0.14 to 0.16 per cent sugar, but in eleven other cases the sugar was between 0.2 and 0.3 per cent., and the duration was also longer.

Sugar is always excreted after the glucose test, even in mild diabetes. In the three tests made by Hamman and Hirschman it was 3, 6.8 and 7 gm., respectively. Williams found from 1 to 10 gm. sugar excreted in the urine. In normal persons, after taking 100 gm. glucose, sugar is sometimes found in the urine, and sometimes not; the total quantity is very small, usually less than 1 gm.

TABLE 5.—SUGAR IN BLOOD DURING FAST

Sugar, per Cent.	Cases Which Excreted No Sugar	Cases Which Excreted Sugar
0.06 - 0.07 .....	—	2
0.07 - 0.08 .....	3	3
0.08 - 0.09 .....	10	6
0.09 - 0.10 .....	3	11
0.10 - 0.11 .....	3	9
0.11 - 0.12 .....	1	1
0.12 - 0.13 .....	—	1

In the glucose test it is necessary to consider the nutrition, the body weight of the individual, the absorption power of the intestine and the decomposition of sugar in the intestines or in the blood. It is especially essential to consider the absorption power of the intestines, although this has been neglected in the past. In our experiment we gave 100 gm. glucose, dissolved in 150 c.c. water in the morning after the fast over night. The individuals weighed from 42 to 63 kg., so that from 2.3 to 1.6 gm. glucose were given per kilo of body weight. Among the fifty-three adults, twenty did not excrete sugar in the urine after taking the glucose. The quantity of sugar excreted by the remaining thirty-three subjects was very small, between 0.25 and 0.795 gm.

In Table 1 are shown the cases which did not excrete sugar in the urine after taking glucose. In Table 2 are shown the cases which did excrete sugar after taking glucose. Diuresis was present in some cases and not in others. In Tables 1 and 2 are classified the cases which did not show diuresis, the cases which showed diuresis, and the cases which excreted all the ingested water. The sugar in the blood shown in Table 1 is generally lower than that in Table 2; i. e., the former average is 0.089 per cent. and the latter is 0.093 per cent.

In alimentary hyperglycemia after the glucose test, the highest percentage of the sugar in the blood in the cases in which sugar is not

excreted in the urine is between 0.0114 and 0.185 per cent., the average being 0.142 per cent.

The highest percentage of sugar in the blood in the cases in which sugar is excreted in urine is between 0.128 and 0.196 per cent., the average being 0.160 per cent.

TABLE 6.—THE HIGHEST DEGREE OF ALIMENTARY HYPERGLYCEMIA

Sugar in Blood, per Cent.	Cases Which Excreted No Sugar	Cases Which Excreted Sugar
0.11 - 0.12 .....	4	—
0.12 - 0.13 .....	1	2
0.13 - 0.14 .....	5	3
0.14 - 0.15 .....	1	5
0.15 - 0.16 .....	4	4
0.16 - 0.17 .....	2	5
0.17 - 0.18 .....	1	3
0.18 - 0.19 .....	1	5
0.19 - 0.20 .....	—	1

Table 6 shows that, generally speaking, the highest percentage of alimentary hyperglycemia in the cases which excrete no sugar is comparatively lower than in the cases which excrete sugar. Table 1 shows that the sugar always increases in the blood after the ingestion of glucose, reaching the maximum in from twenty minutes to two hours, and becoming normal again in three hours. But in most cases the maximum is reached in from twenty minutes to one hour.

Cases 9 and 10 (Table 1) show that the sugar in the blood is not normal even after three hours. In the Case 12 it did not increase decisively until the third hour.

In Table 2, in the cases with sugar in the urine, it also reached the highest percentage in from twenty minutes to one and one-half hours. Most of the cases return to normal within three hours. Cases 14, 29 and 31 did not. The last five cases in Table 2 show that the alimentary hyperglycemia is comparatively high and continues for a long time; but there is no abnormal hyperglycemia during the fast.

In Cases 31 and 32, the sugar excreted in the urine amounts to nearly 1 gm. This is relatively large, but the time of excretion was short, the sugar disappearing at the third hour. In Case 31 the hyperglycemia did not return to normal in the third hour. Case 33 excreted sugar till the fourth hour, but the quantity in the urine was relatively small and the sugar in the blood became normal at the third hour.

According to these tests, it is obvious that the carbohydrate metabolism of these five cases is somewhat different from normal, if we consider that the alimentary hyperglycemia normally reaches 0.17 or 0.18 per cent. and becomes normal on the third hour after the glucose is taken.

Table 7 details the alimentary hyperglycemia noted by various authors after ingestion of 100 gm. glucose and their results will be compared with ours.

TABLE 7.—ALIMENTARY HYPERGLYCEMIA AFTER THE INTAKE OF 100 GM. OF GLUCOSE

Authors	No. of Tests (Persons)	Alimentary Hyperglycemia	Sugar Reaction in Urine
Frank.....	7	0.12 -0.18	2 (+)
Bing and B. Jacobsen.....	10	0.098-0.17	
Th. B. Jacobsen.....	14	16 0.12 -0.16	(—)
		78 0.17 -0.227	(+)
Hopkins.....	5	0.14 -0.156	
Graham.....	3	0.09 -0.18	
Hamman and Hirschmann.....	6	0.1 -0.13	2 (+)
		20 0.114-0.185	(—)
		28 0.129-0.196	(+)
Goto and Kuno.....	53	5 0.192-0.231	(+)
		(lowered sugar tolerance)	

TABLE 8.—DIURESIS

Volume of Urine, C.c.	After Glucose Test	
	Cases Which Excreted Sugar	Cases Which Did Not Excrete Sugar
0 - 100.....	2	4
100 - 200.....	6	14
200 - 300.....	6	7
300 - 400.....	4	3
400 - 500.....	—	3
500 - 600.....	1	2
600 - 700.....	—	—
700 - 800.....	1	—

Some authors state that diuresis is often caused in diabetic patients after the glucose intake. In our investigation we classified the cases into three groups: (1) the cases in which diuresis takes place, (2) the cases in which it does not take place, and (3) the cases in which all the intaken water is excreted.

The average of the maximum of the sugar in the blood in cases which show diuresis is lower than in cases with no diuresis; however, the average in both is nearly the same.

## II. RENAL THRESHOLD

The renal threshold for glucose is a very important factor for the study of renal glycosuria and of diabetes. However, this question is generally neglected owing to the difficulty of the investigation.

Jakobsen<sup>11</sup> studied the alimentary hyperglycemia after the intake of glucose in thirteen adults. He found that when the alimentary hyperglycemia was below 0.16 per cent. there was no sugar in the urine.

11. Jakobsen, Th. B.: *Biochem. Ztschr.* **56**:471, 1913.



TABLE 9.—DETERMINATION OF RENAL THRESHOLD FOR GLUCOSE

Fast over night: the first test, glucose 100 gm. + water 250 c.c.; the second test, glucose 50 gm. + water 125 c.c.

No.*	Name	Age	Glucose per Kilo Body Weight (Gm.)	Urine										Blood										Renal Threshold for Glucose									
				Volume, C.c.				Sugar Reaction (Benedict)						Total Excreted Sugar, Gm.																			
				20 Min.	40 Min.	60 Min.	1½ Hr.	Before Test	20 Min.	40 Min.	60 Min.	1½ Hr.	2 Hr.		3 Hr.	4 Hr.	Before Test	20 Min.	40 Min.	60 Min.	1½ Hr.	2 Hr.	3 Hr.										
3	S. T.	28	100	13	4	9	..	..	..	..	+	+	+	+	—	—	—	—	—	—	—	—	—	0.084	0.142	0.125	0.111	0.045	0.070	0.066	0.071	0.175-0.142	
4	N. S.	34	100	18	11	..	..	..	..	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.085	0.147	0.172	0.181	0.134	0.088	0.068	0.071	0.103-0.172
8	N. K.	43	100	..	..	..	..	..	..	..	+	+	+	+	+	±	..	..	..	..	..	..	..	..	0.064	0.169	0.189	0.180	0.087	0.060	0.067	0.068	0.158-0.169
15	T. S.	27	100	12	11	11	..	..	..	..	+	+	+	+	+	±	..	..	..	..	..	..	..	..	0.077	0.135	0.089	0.103	..	..	..	..	0.123-0.135
19	K. K.	21	160	50	81	65	60	..	..	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.088	0.126	0.160	0.123	0.118	0.063	0.076	..	0.142-0.160
21	Y. T.	36	100	50	26	21	58	..	..	..	+	+	+	+	+	±	..	..	..	..	..	..	..	..	0.091	0.127	0.129	0.086	0.100	0.083	0.063	0.071	0.122-0.129
27	L. T.	22	100	..	20	10	14	..	..	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.107	0.134	0.143	0.100	0.106	0.093	0.075	0.073	0.107-0.134
28	L. A.	23	100	50	7	6	..	..	..	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.107	0.161	0.167	0.107	0.150	0.143	0.120	0.083	0.132-0.180
2	L. C.	37	100	33	8	10	..	..	..	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.069	0.172	0.167	0.145	0.172	0.130	0.104	0.104	0.139
10	L. C.	36	100	..	..	..	..	..	..	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.066	0.150	0.155	0.107	0.061	0.040	0.040	0.068	0.150
20	Y. T.	31	100	23	11	8	7	8	..	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.089	0.132	0.132	0.086	0.067	0.063	0.060	..	0.122
25	L. H.	35	100	32	15	26	..	..	..	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.101	0.155	0.148	0.101	0.088	0.105	0.104	0.108	0.146
334	Lower- ed glu- cose tol- erance	O. G.	42	100	..	..	..	..	..	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.094	0.167	0.172	0.230	0.218	0.147	0.173	0.071	0.107-0.230
324	O. S.	31	109	9	7	5	6	7	..	..	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0.120	0.129	0.210	0.210	0.212	0.129	0.091	0.083	0.120

\* Numbers according to Table 2 † Cases with lowered sugar tolerance.

When hyperglycemia was above 0.17 per cent., sugar appeared. Hamman and Hirschman<sup>7</sup> investigated the renal threshold in six persons and found some with a lowered threshold. Foster stated that the threshold is between 0.149 and 0.164 per cent. One of us<sup>1</sup> reviewed these bibliographies in detail. More recently Williams and Humphreys<sup>10</sup> published the results of their investigation.

The renal threshold is not constant in every normal person, and it is often low, according to Hamman and Hirschmann. If the threshold is lowered the increased sugar in the blood after meals rich in carbohydrate will appear in the urine, easily exceeding the threshold. We tried to investigate whether the alimentary hyperglycemia and the renal threshold are normal in cases in which sugar is excreted in the urine after the glucose test. We gave 50 gm. glucose dissolved in 125 c.c. of water to the persons who excreted sugar in the urine, in the same way as with 100 gm. and examined whether sugar is excreted again in the urine, and also the threshold for glucose. Five out of fourteen persons eliminated sugar. These results are shown in detail in Table 9.

TABLE 10.—RENAL THRESHOLD

Normal Threshold, per Cent.	Lowered Threshold, per Cent.
N. S. ....0.163-0.172	T. S. ....0.123-0.135
N. K. ....0.158-0.169	K. K. ....0.142-0.160
I. A. ....0.152-0.180	Y. T. ....0.122-0.129
O. G. ....0.167-0.220	I. S. ....0.139
	I. T. ....0.150
	O. S. ....0.120
	Y. T. ....0.122
	I. H. ....0.146

If we regard from 0.17 to 0.18 per cent. sugar as being normal, the threshold of four people out of the fourteen is normal, and that of the eight people is clearly lowered. The results are shown in Table 10.

In many of the cases in Table 11, in which sugar was eliminated in the urine after the intake of 100 gm. glucose, the carbohydrate metabolism is not affected, except in the five cases mentioned, and some of the former show the lowered threshold for glucose as shown in Table 11. These cases are by no means diabetic, but are a kind of renal glycosuria, because there is no abnormal hyperglycemia, and the excretion of sugar is caused by the lowered renal threshold. If these individuals with lowered threshold should take a diet rich in carbohydrate, sugar might be excreted in the urine. It is believed that the sugar in the blood rises to almost 0.15 per cent. after a Japanese diet, which is chiefly composed of rice and vegetables rich in carbohydrate. Sugar appears easily after such meals if the threshold is lowered below this level of 0.15 per cent.

We next gave cooked rice, according to the Japanese fashion, to the individuals with the lowered threshold in the morning after an all night fast, and examined the sugar in the blood and in the urine. In some cases after the ingestion of 50 gm. glucose the sugar in the blood is higher than when 100 gm. glucose are taken. This is shown in Cases 3, 10 and 27 in Table 9, and in Cases 3 and 27 sugar is excreted after 100 gm. glucose are taken, but not after the ingestion of 50 gm.

TABLE 11.—RICE (COOKED ACCORDING TO JAPANESE FASHION) WAS GIVEN TO THE PERSON WITH LOWERED RENAL THRESHOLD

Name	Cooked Rice, Gm.	Glucose in Urine (Benedict)						Sugar in Plasma, per Cent.						Renal Threshold Tab. 2) %
		30 Min.	40 Min.	60 Min.	1½ Hr.	2 Hr.	2½ Hr.	30 Min.	40 Min.	60 Min.	1½ Hr.	2 Hr.	2½ Hr.	
I. C.	370	—	±	—	—	—	—	0.155	0.150	0.139	0.138	0.106	0.111	0.15
I. C.	370*	—	+	+	±	±	—	0.176	0.160	0.129	0.104	0.128	0.125	0.15
I. S.	370	—	±	±	±	—	—	0.175	0.148	0.127	0.123	0.106	.....	0.139

\* Boiled potatoes.

### III. EXAMINATION OF THE RENAL FUNCTION OF THE INDIVIDUALS WITH THE LOWERED THRESHOLD FOR GLUCOSE

We have stated that the renal threshold for glucose is sometimes lowered in healthy adults. In order to learn whether the renal function of these individuals is normal or not, we made various tests of the renal function.

(1) *Water Test*.—It is generally believed that the normal adult, when one or one and one-half liters of water are taken, eliminates all the water within four hours, the specific gravity of the urine falls to 1.002-1.004; but in the case of persons whose renal function is impaired, the excretion is affected and the specific gravity does not fall decisively. The method is as follows: One or one and one-half liters of water are taken in the morning after an all night fast. The urine is voided before taking water and every thirty minutes afterward. The quantity and specific gravity are determined. The results are shown in Table 12. No difference was noted between the cases with normal and those with lowered threshold.

(2) *The Relation Between Concentration of Urea in the Blood and the Excretion of Urea in the Urine*.—The urea in the blood and in the urine were measured by the Van Slyke and Cullen<sup>12</sup> method, and McLean's urea index was determined.<sup>13</sup> The results are shown in Table 13.

12. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **19**:211, 1914

13. McLean, F.: J. Exper. Med. **22**:212, 366, 1915.

TABLE 12.—WATER-TEST  
Fast over night, 1000 c.c.-1,500 c.c. water at 9 a. m. were taken.

No.*	Name	Age	Body Water		Urine Volume										Total	Specific Gravity (Urine)										Renal Threshold for Glucose
			Wt. Kg.	Int. ke. °C.	10 Min.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	4 Hr.	30 M. 0-1 Hr.	3-4 Hr.	1 Hr.		1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	3½ Hr.	4 Hr.					
28	I. A.	23	51	1,600	148	152	322	290	90	130	90	7	912	317	1,228	9	5	3	4	7	6	8	10	0.132-0.180		
27	I. T.	22	42	1,000	120	300	370	180	90	25	35	15	1,620	196	1,176	11	8	8	8	9	15	15	10	0.167-0.134		
24	N. S.	34	63	1,000	140	392	400	160	25	20	22	10	1,082	177	1,116	10	7	6	8	4	14	7	22	0.163-0.172		
14	T. K.	18	..	1,050	140	350	400	270	18	5	13	12	749	55	1,125	10	7	6	7	18	22	..	24	0.150		
10	L. C.	36	48	1,000	155	370	390	270	150	50	22	15	749	237	977	5	7	6	5	5	13	5	16	0.108-0.169		
8	N. K.	43	49	1,000	150	380	390	230	90	98	20	17	685	155	790	19	11	7	7	11	15	18	..	0.142-0.160		
19	N. T.	21	43	1,500	600	250	780	500	350	30	..	70	1,830	434	2,480	5	4	5	4	6	..	..	..	0.175-0.142		
15	T. S.	27	48	1,500	210	250	290	370	400	200	5	210	1,090	815	1,370	8	6	6	6	4	4	6	..	0.135-0.135		
21	V. T.	56	51	1,500	120	370	280	465	400	65	57	50	1,235	632	1,807	13	5	5	4	5	6	6	..	0.130		
25	L. H.	35	57	1,500	250	310	375	250	380	130	80	35	1,185	545	1,530	8	6	7	6	6	3	5	13	0.146		
7	Y. Z.	42	..	1,500	34	320	400	430	370	175	45	..	1,144	271	1,515	14	6	5	4	4	12	..	10	0.122		
20	Y. T.	31	..	1,500	45	110	265	350	370	275	49	23	765	717	1,482	23	9	6	6	6	9	14	..	0.130		
324	O. S.	21	48	1,000	170	276	340	250	115	25	30	24	1,006	194	1,969	8	5	5	5	10	..	..	..	0.167-0.280		
434	O. G.	42	..	1,500	105	380	370	340	260	250	115	26	1,195	615	1,846	14	6	7	5	6	b	7	..	..		

\* Numbers according to Table 2. † Cases with lowered sugar tolerance.

(3) *The Relation Between the Concentration of the Chlorid in the Blood and Its Excretion in the Urine.*—The chlorid in the blood was measured by Foster's<sup>14</sup> method and the chlorid in the urine by Volhard and Arnold's method. We determined the above mentioned relation by McLean's formula.<sup>13</sup> The results are shown in Table 14.

TABLE 13.—UREA IN BLOOD AND McLEAN'S UREA INDEX

Number (Table 2)	Name	Body Weight	Calculated Volume of Urine per 24 Hours	Specific Gravity	Blood Urea per Liter Blood, Gm.	Urea in Urine		McLean's Index
						Per Liter	Per 24 Hours	
19	K. K.	45.3	8,200	.....	0.29	2.27	18.61	66
10	I. C.	48.0	2,000	1.023	0.39	10.78	21.61	86
28	I. A.	51.0	1,400	1.023	0.29	10.22	14.33	96
3	S. T.	42.6	3,500	.....	0.31	5.63	19.79	101
4	N. S.	63.0	5,600	1.015	0.27	4.75	26.53	113
27	I. T.	41.8	1,000	1.018	0.30	27.9	27.9	340
15	T. S.	47.6	3,300	.....	0.315	9.48	31.24	184
2	I. S.	49.5	6,000	.....	0.28	4.92	29.53	153
21	Y. T.	51.0	6,000	1.018	0.35	6.7	40.23	156
8	N. K.	48.5	600	1.024	0.345	30.38	18.19	165
32	O. S.	47.5	4,800	1.013	0.285	5.09	24.46	138

TABLE 14.—THE RELATION OF THE RATE OF CHLORID EXCRETION (CALCULATED AS SODIUM CHLORID) TO CONCENTRATION IN PLASMA

Number (Table 2)	Name	Body Weight, Kg.	Sodium Chlorid					Threshold
			Per Liter of Urine, Gm.	Per 24 Hours, Gm.	Per Liter of Plasma			
					Calcu- lated, Gm.	Actual, Gm.	Differ- ence, Gm.	
15	J. S.	47.6	3.70	12.2	5.96			
25	I. H.	57.1	12.1	8.15	5.96			
21	Y. T.	51.0	3.5	21.0	6.05			
3	S. T.	42.6	5.4	18.9	6.11			
2	I. S.	49.5	4.2	25.2	6.12			
19	K. K.	45.3	4.07	33.2	6.21			
10	I. C.	48.0	4.0	8.0	5.90	5.62	-0.28	5.34
28	I. A.	51.0	6.6	9.25	5.95	5.93	-0.02	5.60
8	N. K.	48.5	14.0	8.40	6.01	5.92	-0.09	5.53
4	N. S.	63.0	5.0	28.0	6.11	5.62	-0.49	5.13
27	I. T.	41.8	14.9	14.9	6.19	6.10	-0.09	5.51
32*	O. S.	47.5	4.1	19.7	6.07	6.10	+0.03	5.66

\* Subject with lowered tolerance for sugar.

## DISCUSSION

Our investigations show that thirty-three of fifty-three healthy Japanese adults eliminated sugar after having taken 100 gm. glucose, but that the quantity eliminated was very small. Twenty-eight of the thirty-three showed no abnormal hyperglycemia and in some cases the renal threshold for glucose was clearly low. It is clearly evident, when the threshold for glucose is lowered, that the lower the threshold the more easily sugar is eliminated in the urine after a carbohydrate diet. If the threshold is severely affected, then sugar will be excreted

14. Foster, G. L.: J. Biol. Chem. **31**:483, 1917.

in the urine even when the sugar in the blood is normal or very slightly higher than normal.

Since the renal threshold for glucose is sometimes lowered even in some normal persons, we must pay careful attention to the diagnosis of so-called mild diabetes, in which slight glycosuria is present after meals, and in which no clinical symptoms are noted. To diagnose mild diabetes and renal glycosuria, it is necessary to examine not only the excretion of the sugar in the urine, but also the sugar in the blood after the glucose test, and to study the renal threshold for glucose carefully.

#### SUMMARY

In order to investigate the renal threshold for glucose in Japanese, glucose tests were made on fifty-five adults.

1. In the normal adults the sugar in the blood the morning after the over night fast was between 0.066 and 0.166 per cent., in the majority of cases being from 0.08 to 0.11 per cent., with an average of 0.092 per cent.

2. The sugar in the blood nearly always increased after the ingestion of 100 gm. glucose. Thirty-three of the fifty-three persons excreted sugar, although the quantity was very small, between 0.025 and 0.795 gm.

3. Persons who did not excrete sugar averaged 0.089 per cent. sugar in the blood the morning after the over night fast. The majority showed between 0.08 and 0.09 per cent. sugar. The highest percentage of alimentary hyperglycemia after the ingestion of 100 gm. glucose was between 0.114 and 0.185 per cent., the majority excreting between 0.11 and 0.16 per cent., with an average of 0.142 per cent.

4. Persons who excreted sugar averaged 0.093 per cent. sugar in the blood in the morning after the over night fast. The majority excreted between 0.08 and 0.11 per cent. The highest percentage of alimentary hyperglycemia after ingesting 100 gm. glucose was between 0.128 and 0.196 per cent., the majority excreting between 0.14 and 0.19 per cent., the average being 0.160 per cent.

5. No matter whether sugar is excreted in the urine or not, the alimentary hyperglycemia reached the maximum between forty and sixty minutes after the test and becomes normal within the three hours.

6. Five persons who excreted sugar showed an abnormal hyperglycemia. The increase of sugar in the blood was quite high, 0.2 per cent., and the excretion of sugar in the urine was greater than in the other cases. Some of them showed a hyperglycemia of longer duration. However, these five individuals had neither hyperglycemia in the morning, nor any diabetic symptoms.

7. Eight of the fourteen subjects who excreted sugar after the glucose test had a lowered threshold for glucose as follows: 0.122 to 0.129 per cent., 0.120 per cent., 0.122 per cent., 0.123 to 0.135 per cent., 0.139 per cent., 0.142 to 0.160 per cent., 0.146 per cent. and 0.160 per cent.

8. The renal function of those individuals whose renal threshold for glucose was lowered was normal for the excretion of water, urea and chlorids.

9. Glycosuria appears sometimes even in normal persons owing to the lowered threshold for glucose, without any disturbance of carbohydrate metabolism. Therefore, we must pay careful attention to the differentiation of so-called mild diabetes and renal glycosuria.<sup>15</sup>

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15. The following references may also be consulted:

Naunyn: *Der diabetes mellitus*, 1906.

Bang, I.: *Methoden zur Mikrobestimmung einiger Blutbestandteile*, Wiesbaden, 1916.

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## THE EFFECT OF ANTISYPHILITIC TREATMENT ON THE COLLOIDAL GOLD REACTION \*

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Since the first presentation of the colloidal gold reaction by Lange<sup>1</sup> in 1912, both its technic and significance have been discussed at great length in the current medical literature, particularly in Germany and this country, until it has now an undisputed place in the routine examination of spinal fluids as a definite aid to the diagnosis of many affections of the central nervous system.

A perusal of the voluminous literature on this subject discloses a noticeable absence of attention given to the effect of antisiphilitic treatment on this very important reaction. Our information on this subject comes largely from chance comments interspersed at various points in general discussions of the colloidal gold reaction by different authors. And, after compiling these various bits of information, one is impressed by the great variance of opinion expressed and the lack of proof or detailed discussion advanced as a basis for such opinions.

In a previous publication I (with Nixon)<sup>2</sup> reviewed this phase of the subject in a general discussion of the colloidal gold reaction, and at that time decided that it was worthy of a more detailed and prolonged consideration.

Lange<sup>1</sup> in his first presentation of the test claimed that its results closely paralleled the clinical course of syphilitic disease of the central nervous system. Eskuchen<sup>3</sup> noted a general parietic curve change to a syphilitic one. Solomon and Koefod<sup>4</sup> found one case of tabes in which five spinal fluids were examined at intervals of several days during intraspinal treatment and the curve changed only from 02222-10000 to 0012222100. Six other fluids behaved in practically the same manner, hence they concluded that there was no marked change in treated cases and no relation between the curve and duration or severity of the disease.

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1. Lange: Die Ausflockung kolloidalen Goldes durch Cerebrospinalflüssigkeit bei luetischen Affektionen des Zentralnervensystem, *Ztschr. f. Chemotherap.* **1**:44, 1912.

2. Warwick and Nixon: The Colloidal Gold Reaction and Its Clinical Interpretation, *J. Exper. Med.* **25**:119, 1920.

3. Eskuchen: Die fünfte Reaktion, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **25**:486, 1914.

4. Solomon and Koefod: Experience with Lange's Colloidal Gold Test in 135 Spinal Fluids, *Boston M. & S. J.* **173**:996, 1915.



Swalm and Mann<sup>5</sup> noticed that in remissions and after-treatment a paretic curve might be lost or changed to one of the syphilitic type. Black, Rosenberg and McBride<sup>6</sup> observed a tendency for vigorous intravenous or intraspinal treatment to bring all positive tests toward the negative side, but noted that the colloidal gold reaction was the last to turn negative, and thus was the most reliable as a prognostic guide. They saw a paretic curve during treatment change to a syphilitic curve and later to a meningitic curve, while the Wassermann reaction changed from positive to negative. They concluded that although the colloidal gold curve is the last to become negative, it does so only after a clinical cure. Mehrtens<sup>7</sup> thought that the reaction steadily decreased and became atypical under treatment. De Crinis and Frank<sup>8</sup> noted that as a patient improved, the colloidal gold curve returned to normal. Farnell<sup>9</sup> found some paretic curves becoming atypical under treatment while others remained typical, and some tabetic curves decreased in intensity. Hammes<sup>10</sup> mentioned five cases with antisyphilitic treatment in which the colloidal gold reaction changed but in only one did it become negative. Miller and Levy<sup>11</sup> concluded that it was possible that this test, in comparison with those used formerly, might prove to be more sensitive as an indicator of the results of specific therapy in syphilitic diseases of the central nervous system.

Miller, Brush, Hammers and Felton<sup>12</sup> had one case of paresis in which, after an extensive course of treatment, a negative curve resulted, but this was the only one returning to normal. Two tabetic curves, however, became negative under treatment and others became atypical. Ayer<sup>13</sup> concluded that all spinal fluid tests are without value in indicating progress under treatment. Grulee and Moody<sup>14</sup> reported one case of congenital syphilis in a patient three weeks of age, in which a positive colloidal gold reaction, under treatment, became negative at

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5. Swalm and Mann: The Colloidal Gold Test on Spinal Fluid in Paresis and Other Mental Diseases, New York M. J. **101**:719, 1915.

6. Black, Rosenberg and McBride: The Colloidal Gold Test, J. A. M. A. **69**:1855 (Dec. 1) 1917.

7. Mehrtens: Discussion, Calif. State M. J. **16**:170, 1918.

8. De Crinis and Frank: Ueber die goldsol reaktion im Liquor cerebrospinalis, München. med. Wchnschr. **61**:1261, 1914.

9. Farnell: Observations on the Colloidal Gold Reaction, Providence M. J. **16**:158, 1915.

10. Hammes: The Comparative Value of the Wassermann, the Colloidal Gold and Other Spinal Fluid Tests, Am. J. M. Sc. **154**:625, 1917.

11. Miller and Levy: The Colloidal Gold Reaction in the Cerebrospinal Fluid, Bull. Johns Hopkins Hosp. **25**:133, 1914.

12. Miller, Brush, Hammers and Felton: A Further Study of the Diagnostic Value of the Colloidal Gold Reaction, Together with a Method for Preparing the Reagent, Bull. Johns Hopkins Hosp. **26**:391, 1915.

13. Ayer: Rational Use of Spinal Puncture, J. Nerv. & Ment. Dis. **46**:429, 1917.

14. Grulee and Moody: Lange's Gold Chlorid Test on the Cerebrospinal Fluid in Congenital Lues, J. A. M. A. **61**:13 (Nov. 22) 1913.

six weeks and they concluded that treatment modified the reaction but to a less degree than it did the Wassermann. Kaplan and McClelland<sup>15</sup> noted a persistence of the curve in well treated cases and suggested that it might be analogous to the "Wassermann-fast" condition. Solomon and Southard<sup>16</sup> thought that the colloidal gold reaction might remain positive after all the other tests became negative, or at times the colloidal gold and Wassermann reactions might both persist. In their series they saw three cases with negative colloidal gold reactions, while the other tests were positive, hence concluded that changes in the tests do not parallel the clinical condition of patients. Solomon, Koefod and Welles<sup>17</sup> found that after intradural or intravenous treatment only slight curves may show. One typical paretic after three weeks' treatment with mercury gave a curve of 0011100000. Lee and Hinton<sup>18</sup> considered that cases having had arsphenamized serum did not give uniformly typical gold curves.

Lowrey<sup>19</sup> noted paretic curves becoming syphilitic in type and later said<sup>20</sup> that serologic findings might definitely increase under treatment with or without corresponding clinical signs, thus emphasizing the importance of the provocative reaction in rare cases. He also stated that a negative spinal fluid is not absolutely conclusive evidence of the absence of neurosyphilis. Robertson<sup>21</sup> thought that the character of the curve varied with the clinical improvement or regression of each case, and cited two cases of tabes with curves becoming negative. Sanborn<sup>22</sup> said that the intensity of the curve diminishes with successive treatments. Vogel<sup>23</sup> noted five cases of tabes under intraspinal treatment showing a distinct flattening of the curve in correspondence to the patient's clinical condition and concluded that the colloidal gold test is the most sensitive indicator of the changes in the central nervous system.

Contemplation of this wide variability of the opinion of different authors leads to a justifiable confusion of ideas, but some elucidation

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15. Kaplan and McClelland: The Precipitation of Colloidal Gold, *J. A. M. A.* **62**:511 (Feb. 14) 1914.

16. Solomon and Southard: Notes on Goldsol Diagnostic Work in Neurosyphilis, *J. Nerv. & Ment. Dis.* **45**:230, 1917.

17. Solomon, Koefod and Welles: The Diagnostic Value of Lange's Goldsol Test, *Boston M. & S. J.* **173**:957, 1915.

18. Lee and Hinton: A Critical Study of Lange's Colloidal Gold Reaction in Cerebrospinal Fluid, *Am. J. M. Sc.* **148**:33, 1914.

19. Lowrey: Cerebrospinal Fluid Tests, Especially the Gold Reaction in Psychiatric Diagnosis, *J. Nerv. & Ment. Dis.* **46**:186, 1917.

20. Lowrey: Further Observations on Neurosyphilis and the Psychoses, *Arch. Neurol. & Psychiat.* **3**:500, 1920.

21. Robertson: Discussion, *Boston M. & S. J.* **174**:136, 1916.

22. Sanborn: Discussion. *Ibid.*

23. Vogel: The Nature and Interpretation of the Colloidal Gold Reaction, *Arch. Int. Med.* **22**:496 (Oct.) 1918.

may be brought about by the introduction and discussion of a few fundamental conditions. First, it is an accepted fact in most laboratories that an absolutely standard solution of colloidal gold cannot be prepared. It may answer all requirements usually made<sup>2</sup> yet with equally satisfactory but different solutions one may obtain slightly different curves with the same spinal fluid. These different curves, however, fall into the same zones and are relatively the same, varying only in intensity. Therefore, one must expect that curves in treated cases may vary somewhat because of the different solutions necessarily used. Second, it must be borne in mind that one may meet all types of curves varying from those on the borderline or practically negative to very definite, well marked curves. It is easy to understand, therefore, that the worker dealing with a marked, well established curve may arrive at an opinion very different from that of another observer concerned chiefly with low curves and patients tested comparatively early in the course of their disease. Third, only by a detailed and careful study of a considerable number of cases under carefully noted treatment is one justified in arriving at any definite conclusion. Conclusions indicated by a small series of cases may be overthrown entirely by further observations.

At the University Hospital the usual method of treatment consists of intravenous injections of arsphenamin (recently of neo-arsphenamin) followed by spinal drainage twenty minutes later, given at intervals of from five to seven days. This method yields frequent spinal fluids for examination during the course of treatment, and, therefore, makes possible the detailed study suggested. These arsphenamin treatments were usually preceded or accompanied by mercury in the form of "rubs" or intramuscular injections. A few of the earlier cases received arsphenamized serum intraspinally. These cases are noted in the tables. Occasionally, for various reasons, drainage was not done, or the fluid obtained was bloody and not fit for routine examination, thus causing an apparent wide gap between spinal fluids examined. Also occasionally a patient received treatments outside the hospital and consequently a complete record was not always available.

The accompanying tables represent graphically the results obtained in this study. They have been abridged as much as possible, particularly the clinical notes, but the main facts on which the diagnosis was based are given. The Wassermann tests were made under the supervision of Dr. W. P. Larson, chief of the department of bacteriology, but the other laboratory tests were performed by myself according to the technic described in an earlier publication,<sup>2</sup> thus eliminating, as far as possible, the personal equation.

By curves in Zone I, the so-called "paretic zone," are meant curves showing their maximum intensity in the first five tubes, the higher dilu-

TABLE 1

Case No. Diagnosis	Date	Nome	Wasser- mann	Cells	Colloidal Gold	Mercury	Arspheamin	Age	Infection	Duration	Clinical Findings	Result
17638 Tubes	11/10/19	+	+	30	554532100	None	4 intravenous 11/10/19 to 11/25/19	50	?	8 mos.	Girdle sensation; weakness and numbness of extremi- ties; incontinence of urine; stumbling in dark; hypal- gesia; double; Argyll Rob- ertson pupils	Improved
	11/11/19	+	+	100	000000000							
	11/12/19	+	+	17	000000000							
	11/26/19	+	+	?	554331000							
17307 Tubes	9/23/19	+	+	12	5555554321	None	4 intravenous 9/23/19 to 10/11/19	52	1909	2 yrs.	Urinary incontinence; un- equal and irregular pupils; Argyll Robertson pupils; unequal and sluggish knee jerks	Improved
	9/30/19	+	+	?	5555432100							
	10/6/19	+	+	12	2223331000							
	10/12/19	+	+	9	5544331000							
16920 Cerebro- spinal syphilis	7/21/19	+	+	2	0001210000	Rubs	0 intravenous 7/31/19 to 9/2/19	51	1886	1 yr.	Apraxia, loss of memory; weakness of right arm; transient unconsciousness; irregular pupils with slug- gish, light reaction; + Ba- binski on right	Improved
	7/31/19	+	+	1	0000000000							
	8/4/19	—	—	2	0000000000							
	8/26/19	—	—	9	0000000000							
18771 Tubes	12/15/19	++	—	?	0001231000							
	4/29/20	+	+	1	0001211000	None	8 intravenous 5/1/20 to 6/22/20	50	?	2 mos.	Difficulty in speech and writing; weakness in hands and left foot; numbness of hands and feet; nerve deafness; + Rhomberg; impaired coor- dination	
	5/5/20	+	+	1	0001110000							
	5/12/20	+	+	1	0000000000							
19080 Tubes	5/21/20	+	+	?	0000000000							
	5/26/20	+	+	?	0000000000							
	6/6/20	+	+	1	0000000000							
	6/15/20	+	+	1	0000000000							
19080 Tubes	6/24/20	++	—	?	0012000000	Some previous sulfate injections, 5/31/20 to 6/9/20	Some previous treatment 0 intravenous 5/28/20 to 6/24/20	32	1911	2 yrs	Numbness of hands and feet; constant walking in dark; impaired vision; girdle sen- sation; unequal, irregular pupils; no reaction to light; hypalgesia over nose and cheeks; band of anal- gesia across chest; vibra- tion sense absent in toes; Romberg; knee jerk, 0; ankle jerk, 0	
	5/25/20	+	+	40	1112100000							
	5/28/20	+	+	200	1112220000							
	6/2/20	+	+	36	0001211000							
19080 Tubes	6/6/20	+	+	30	1112110000							
	6/12/20	+	+	20	0000310000							
	6/18/20	+	+	40	0002211000							
	6/24/20	+	+	15	0011200000							
19080 Tubes	6/29/20	+	+	15	0000000000							
	7/5/20	+	+	15	0001110000							
	7/12/20	++	+	25	0001100000							
	7/19/20	++	+	5	0000110000							

TABLE 2

Case No. Diagnosis	Date	Nonce	Wasser- man	Cells	Colloidal Gold	Mercury	Asphenamin	Age	Infe- ction	Duration	Clinical Findings	Result
18184 Parasitis	1/24 '20	++	+	70	5555329110	None	4 intravenous 2/20 '20 to 2/23/20	45	?	4 yrs.	Right sided paralysis; un- equal pupils; Argyll Rob- ertson reaction; hyper- active knee jerk; splinter disturbances	No improvement
	2/2 '20	++	+	21	5555333110							
	2/11/20	++	+	38	5555443210							
	2/20/20	++	+	?	5544332200							
	2/14/20	—	+	4	0001221000	Mercury sali- cylate in- jections from 3/4 '20 to 3/31/20	6 intravenous 3/1/20 to 3/29/20	22	1918?	?	Impaired vision; choroid- itis; detachment retina	Improved
18296 Syphilis?	3/10/20	—	—	4	0000000000							
	3/27/20	—	—	3	0000000000							
	2/28 '20	+	+	60	5555322100	13 mercury salicylate in- jections from 3/4 '20 to 4/17/20	8 intravenous 3/1/20 to 4/21/20	35	1910	7 yrs.	Numbness of legs and ulnar side of arm; sharp pain in chest; ptosis; impaired sensation over nose, face across chest; Achilles jerk, 0	Improved
	3/29 '20	—	—	7	0044225000							
	4/3/20	—	—	12	1113106000							
18759 Tuberc	4/13/20	++	—	12	0022106000							
	4/17/20	++	—	12	0022106000							
	4/21/20	++	—	2	0021060000							
	2/11/20	—	+	3	0011290000	6 mercury salicylate in- jections from 3/4 '20 to 3/27/20	Treatment in 1917; 3 intra- venous 3/1/20 to 3/15/20	37	?	3 yrs.	Gastric crises; weakness; unable to walk; unequal pupils; Argyll Robertson reaction; hypalgnesia over nose; hypotonus; knee jerk, 0; ankle jerk, 0	No improvement
	2/17 '20	—	+	?	0001060000							
18072 Tuberc	2/25 '20	—	+	8	0000000000							
	3/11 '20	—	+	5	1113421100							
	1/6/20	+	+	15	1134431000	None here; 6 injections of mercury and arsenic previously	4 intravenous 1/12/20 to 2/2/20	44	?	1 yr.?	Weakness; pain in arms and legs; strabismus; ir- regular pupils; Argyll Robertson reaction; dimi- nished knee jerk; ankle jerk, 0	Improved
	1/19/20	+	—	15	1123106000							
	1/26/20	+	—	15	1123300000							
17905 Tuberc	2/2 '20	+	—	5	0112311100							
	12/17 '19	++	+	50	1445333000	None here; some early in 1919	4 intravenous 12/19/19 to 1/7/20	41	?	1 yr.	Weakness of legs; pro- trude vomiting; severe head- aches; irregular pupils; + Rhombberg	Slight improve- ment
	12/27 '19	+	+	70	0222100000							
	12/27 '19	+	+	50	1123331000							
	12/27 '19	+	+	50	1123331000							
17811 Tuberc	12/1/19	++	+	6	0012210000	None	5 intravenous 12/4 '19 to 12/27 '19	54	1895	3 yrs.	History of paralysis for 1 month; unequal, sluggish knee jerks; Achilles jerk, 0; unequal, irregular pupils	No improvement
	12/8/19	++	—	1	0000000000							
	12/13/19	++	+	3	0013311000							
	12/30/19	++	+	6	0012100000							
	12/30/19	++	+	6	0012100000							
17785 17924 Tuberc	11/28/19	++	+	?	1234422000	None	1 intravenous 12/1/19	43	?	6 mos.	Primary optic atrophy; incontinence of urine; stumbles in dark; fixed and irregular pupils; knee jerk, 0; diminished pain sense in calves; + Rhom- berg	No improvement
	12/1/19	++	+	100	1233331100							
	12/17/19	++	+	35	1123106000							
	12/17/19	++	+	24	1112210000							
	12/20/19	+	+	24	1112210000							

TABLE 3

Case No. Diagnosis	Date	Nome	Wassermann	Cells	Colloidal Gold	Mercury	Arsphenamin	Age	Infection	Duration	Clinical Findings	Result
134-8 Tabes dorsalis	12/31/15 4/7/16 2/27/16 2/3/16 3/13/18	± ± ± ± —	++ ++ ++ —	7 1 1 1 1	5555554000 2233332900 1233332000 1133210000 1121160000	Rubs. 1/20/16 to 5/16/16; some later	14 intravenous, 2 intraspinal; more at dis- pensary	28	....	5 yrs.	Numbness of hands; atro- phy of hand muscles; shooting pains in extremi- ties; knee and ankle jerks absent; loss of deep sensa- tion in the extremities	Marked improve- ment, but not permanent
7655 Tabes dorsalis	3/29/16 4/7/16 5/3/16 5/8/16 6/9/16 1/23/16 1/14/17	± ± ± ± ± — ±	++ ++ ++ ++ ++ —	? ? 6 1 1 2 3	1122211000 4443332000 1122160000 0011000000 0134221100 1111000000 0033250000	1 1/20/16 to 5/16/16; some later	4 intravenous 3/27/16 to 1/8/17; 2 intraspinal 11/22/16 to 1/10/17	51	?	.....	Progressive muscular at- rophy; shooting pains; sphincter disturbances; Argyll Robertson pupil; Charcot's joints; incoordi- nation	A little improve- ment, but tem- porary
6797 Cerebro- spinal syphilis	4/21/16 9/2/16 10/23/16	± ++ +	++ — —	10 7 3	1312533210 0000000000 0000000000	None	5 intravenous 11/29/15 to 10/20/16; 3 intra- venous 9/2/16 to 10/22/16	40	1910	1 yr.	+ Rhombic; ankle clonus; ataxia; headaches; severe dizzy spells; frequent irri- tation	Improved
8870 Tabes	6/15/16 8/23/16	± +	++	7 ?	5544210000 2211000000	.....	Many previous injections; 3 intravenous 7/24/16 to 8/16/16	37	1902	9 yrs.	Shooting pains; difficulty in walking; girdle sensation; sphincter disturbances; Argyll Robertson pupils	No improvement
9726 Tabes dorsalis	10/11/16 11/1/16	++ ++	++ ++	? 48 18	5522200000 5533332000 5443200000	Rubs. 10/21/15 to 12/1/16	1 intravenous 11/9/16; 3 intraspinal 10/26/16 to 11/20/16	39	....	.....	Diplopia; shooting pains; sphincter disturbances; Argyll Robertson pupils; knee jerks and ankle jerks absent	Improved
16916 Tabes dorsalis	7/17/19 9/28/19 8/7/19 8/11/19	± — — —	— — — —	12 5 2 6	0000000000 0000000000 0000000000 0000000000	2 injections of salicylate; rubs. 7/23/19 to 8/23/19	5 intravenous in April, 1919; 8 intravenous 7/28/19 to 8/20/19	39	1902?	1 yr.	4 blood Wassermann; girdle sensation; can't walk in dark; shooting pains; atrophied hand muscles; Charcot knee; knee and ankle jerks absent; inco- ordination	No improvement objectively, bet- ter subjectively
16942 Tumor of meninges confirmed at necropsy	7/19/19 7/28/19 8/7/19 8/11/19 8/15/19	++ ++ ++ ++	— — — —	12 2 1 1 1	0013333110 0112332220 0001231000 0000120000 0000122111	Rubs. 7/25/19 to 8/14/19	4 intravenous 8/7/19 to 8/21/19	59	?	.....	Girdle sensation; incoordi- nation; numbness of legs; irregular and sluggish pup- ils; knee and ankle jerks absent	Died

TABLE 4

Case No. Diagnosis	Date	Nonne	Wassermann	Cells	Colloidal Gold	Mercury	Arsphenamin	Age	Infection	Duration	Clinical Findings	Result
1366 Tabes paresis	8/21/16	+	+	11	555430000	Rubea 8/13/16 to 8/31/16	4 intravenous 9/1/16 to 10/1/16; 39 intravenous 12/27/18 to 10/9/19; continued at dispensary	39	?	.....	Argyll Robertson pupils; Wassermann; knee jerk absent; psychie disturbances	Marked improve- ment
	12/30/18	+	+	18	555430000							
	1/24/19	+	+	1	444330000							
	2/1/19	—	+	1	444330000							
	2/8/19	—	+	3	023320000							
	4/28/19	—	+	4	555431000							
	5/5/19	—	+	?	555431000							
	5/19/19	+	+	3	555431000							
	6/13/19	+	+	0	555431000							
	6/18/19	+	+	1	555431000							
	6/27/19	+	+	1	555431000							
	7/29/19	+	+	1	555431000							
	8/12/19	—	+	2	555431000							
1351 Tabes dorsalis	9/18/19	—	+	6	555431000							
	10/7/19	+	+	?	555431000							
	10/10/19	+	+	1	555431000							
	1/17/20	+	+	2	444331000							
	3/4/20	+	—	5	554443000							
	3/26/20	+	+	2	5555511000							
	11/1/17	+	+	80	455555544	Noce	3 intravenous 11/25/17 to 4/22/19, and some unknown	37	1900	2 yrs.	Unequal pupils; Argyll Rob- ertson pupils; impaired sensation over chest; + blood Wassermann; tibial exostosis	Improved
1368 Cerebro- spinal syphilis	9/19/19	—	+	1	001222000	Salicylate 7 injections 3/8/19 to 9/4/19	9 intravenous 2/26/19 to 8/25/19	32	?	.....	Nerve deafness; unilateral primary optic atrophy; unequal pupils; knee jerks unequal; + blood Wasser- mann	Improved
	7/17/19	—	—	2	001321000							
	10/6/19	+	—	1	000000000							
17307 Tabes dorsalis	9/23/19	+	+	12	555554321							
	9/30/19	+	+	?	5555432100							
	10/6/19	+	+	12	222331000							
1368 Tabes dorsalis	10/12/19	+	+	9	5544331000							
	10/20/17	—	—	6	000000000	19/25/17 to 11/8/17 and 11/28/17 to 12/6/17	12 intravenous 1/15/19 to 3/12/19	33	....	3½ yrs.	Primary optic atrophy; headaches; impaired vis- ion; knee jerk absent; ankle jerk absent; urine slow in starting	No improvement
	1/19/19	—	+	49	224431000							
	1/22/19	—	+	23	013210000							
	1/30/19	—	+	15	012310000							
	2/5/19	—	+	?	1223210000							
	2/12/19	+	+	10	1112230000							
	2/19/19	+	+	5	001322000							
	2/22/19	+	+	12	354333311							
	3/6/19	+	+	16	1223310000							

TABLE 5

Case No. Diagnosis	Date	Nonne	Wassermann	Cells	Colloidal Gold	Mercury	Arsphenamin	Age	Infection	Duration	Clinical Findings	Result
10850 Cerebro- spinal syphilis	7/7/19 7/15/19 7/21/19	++ ++ ±	+ — —	1 9 5	001230000 001344100 001333100	None	3 intravenous 7/15/19 to 7/25/19	29	1913	.....	Headaches; psychic disturbances; irregular pupils; jerks; ocular palsies; sluggish; + blood Wassermann	General improvement
15547 Cerebro- spinal syphilis	12/31/18 2/6/19 2/14/19	+ ++ ±	? ++ ++	14 ? ?	334333100 012332100 443332100	None	8 intravenous 12/13/18 to 2/14/19	34	1914	.....	Argyll Robertson pupils; other signs complicated by postdiphtheric paralysis; + blood Wassermann	Marked improvement
10840 Cerebro- spinal syphilis	7/7/19 7/15/19 7/21/19 7/25/19 7/29/19 8/2/19 8/4/19	++ ++ ++ ++ ++ ++ ++	+ ++ ++ ++ ++ ++ ++	45 20 24 18 25 15 8	002555553 014555541 001441040 001221600 001222100 002226000 000122000	Rube. 7/15/19 to 8/7/19	6 intravenous 7/15/19 to 8/7/19	48	1891?	.....	Argyll Robertson pupils; atrophy of muscles; + Romberg; + blood Wassermann; knee jerks hyperactive	Improved
17330 Cerebro- spinal syphilis	9/19/19 9/23/19 9/30/19 10/6/19 10/12/19	++ ++ ++ ++ —	+ ++ ++ ++ —	82 30 ? 9 ?	3322110000 335543100 223432100 002221000 000000000	None	4 intravenous 9/23/19 to 10/11/19	32	?	.....	Fixed pupils; unequal pupils; ptosis; paralysis left extra ocular muscles; + blood Wassermann	Improved



TABLE 6

Case No. Diagnosis	Date	Nonne	Wasserman	Cells	Colloidal Gold	Mercury	Asphenanula	Age	Infection	Duration	Clinical Findings	Result
15603 Tuberculous dorsalis	1/18/19	—	—	6	0/8 0/00000	None	9 intravenous 1/24/19 to 5/10/19	53	?	3 yrs.	Gastric crises; parasthesia of extremities; irregular and unequal pupils; knee jerk diminished; + Rhom- berg; slight incoordination of extremities; no vibra- tion sense in feet	Improved
	2/6/19	—	—	2	0/8 0/00000							
	2/14/19	+	—	2	0/8 0/00000							
	2/24/19	—	—	2	01/2220000							
	3/7/19	+	—	1	11/2330000							
	3/9/19	—	—	1	11/2220000							
	3/19/19	—	—	2	0/00000000							
15857 Tuberculous dorsalis	4/15/19	—	—	1	0/013310000							
	5/12/19	—	—	3	0/00000000							
	5/22/19	+	—	3	11/23310000							
	1/24/19	—	—	15	0/000000000	Rube, 4/4/19 to 4/31/19	7 intravenous 2/3/19 to 4/31/19	44	1919?	2 yrs.	Gastric crises; irregular pa- pils; Argyll Robertson pupils; sluggish knee jerks; ankle jerks sluggish and unequal	Some improve- ment
	2/14/19	—	—	30	0/000000000							
	2/24/19	—	—	10	22/333200000							
	3/1/19	—	—	8	12/333310000							
16137 Tuberculous dorsalis	3/1/19	+	—	22	0/000000000							
	3/8/19	+	—	27	0/000000000							
	3/15/19	+	—	?	44/3332000							
	3/8/19	—	—	1	0/8 0/0000000	None	4 intravenous 3/15/19 to 4/16/19	51	?	.....	Irregular and unequal pa- pils; Argyll Robertson pupils; knee jerk absent; + Rhomberg; no vibra- tion sense in feet	Improved
	3/15/19	—	—	0	0/000000000							
	3/24/19	—	—	1	0/000000000							
	4/2/19	—	—	0	0/000000000							
16556 Tuberculous dorsalis	4/16/19	—	—	1	0/8 0/0000000							
	6/3/19	—	—	12	0/0133310000	Some before; 6/6/19 to 6/29/19	Previous gen- eral treatment for 1½ yrs.; 2 intravenous 6/12/19 to 6/18/19	57	1887	.....	Incontinent; Argyll Robert- son pupils; knee jerk ab- sent; + Rhomberg; con- stipation; diagnosis con- firmed at necropsy	Died
	6/18/19	+	—	6	0/003322100							
	2/21/19	—	—	3	0/000000000	Rube, 2/21/19 to 3/31/19	7 intravenous 3/1/19 to 5/12/19	40	?	8 yrs.	Unsteady gait; incont- inence; irregular and un- equal pupils; no vibration sense in legs; hyperactive knee jerks; double Bab- insky; unsteady gait; pain around abdomen; relaxa- tion around joints	Marked improve- ment; able to walk and con- trol sphincters
	3/6/19	—	—	0	0/012220000							
	3/22/19	+	—	7	0/001220100							
	3/31/19	+	—	13	22/3331000							
15900 Cerebro- spinal syphilis	3/31/19	+	—	1	0/002291000							
	4/8/19	+	—	1	23/444500	6/2/19 to 6/17/19						
	4/16/19	—	—	8	23/444500	3 injections						
	5/5/19	—	—	1	22/33311000							
	6/16/19	—	—	1	0/000000000							
	1/19/18	+	—	30	12/222109000	None	7 intravenous 1/26/18 to 3/4/18	58	?	.....	Absent knee jerks; sluggish pupils; difficulty in start- ing urine	Improved
	1/26/18	—	—	30	11/333320000							
	2/14/18	+	—	6	0/002210000							

tions, such as 5555543100, which are usually found in cases of paresis and also quite frequently in cases of multiple sclerosis. By curves in Zone II, the so-called "syphilitic zone," are meant those showing no change in the highest dilutions but appearing and reaching a maximum in the center, as 0023311000, usually seen in tabes and cerebrospinal syphilis and occasionally in multiple sclerosis. The last five tubes constitute Zone III, or the so-called meningitic zone, and here appear the numerous "irritative" curves associated with tumors of the brain or spinal cord, myelitis or meningitis of the various types.

In this series fluids from 35 patients were observed under more or less intensive treatment. Of these, two showed no curves, leaving only thirty-three curves that were studied. Such a series, particularly as a few were observed only for a short time, is still too small to enable one to reach any absolutely definite conclusions regarding the effect of antisyphilitic treatment on the colloidal gold reaction. However, some very significant facts are brought out.

All of these fluids may roughly be divided into three classes: (1) those showing no change under treatment; (2) those decreasing in intensity or becoming negative and (3) those increasing in intensity. Such a division is, of course, arbitrary and somewhat unsatisfactory, as many fluids are on the borderline between the classes, but, in spite of that fact, it will give a better idea of the results obtained than a consideration of the tables as a whole. In Class 1, if we consider the last examination (which represents only the cessation of spinal punctures and not the terminal condition of the fluid) we find nine fluids, or 27 per cent., remaining unchanged. In Class 2, seventeen fluids or 51.5 per cent., decrease in intensity, and in Class 3, seven fluids, or 21.5 per cent. increase in intensity.

Therefore, judging from this limited series, one is justified in the assumption that the majority of the colloidal gold curves do actually decrease in intensity after treatment. At the same time, however, one must note that of these thirty-three curves only five, or 15 per cent., came down to an absolute negative, and even in these five one must admit the possibility of the reappearance of the curve if later fluids had been examined. On the other hand, one is confronted by the possible inadequacy of the treatment, and it must be admitted that, if continued often enough, the colloidal gold curves might have become permanently negative. However, with the figures at hand one is justified in making the statement that even though the colloidal gold curve decreases during treatment it very rarely disappears entirely.

The results of these tables point to the fact that, in general, the more pronounced curves, particularly in Zone I, resisted the effect of treatment to a much more marked degree than did those of Zone II.

The less pronounced curves responded to treatment and more readily returned to normal. But in these last cases no more and frequently much less clinical improvement was noted than in those having more pronounced curves which so successfully resisted treatment. For example, Case 15695 showed very marked clinical improvement and by keeping up treatment at the dispensary the patient was enabled to live a fairly normal and useful life for a number of years, yet her spinal fluid showed at all times a pronounced curve and usually a positive Wassermann. While this illustrates very well the discrepancy between clinical improvement and spinal fluid findings, it points very definitely to the fact that, although clinical improvement was marked, a cure had not been effected and treatment could not be discontinued—a fact borne out by clinical symptoms. On the other hand, Case 16137 was a patient who was bedridden and helpless, while his fluid was entirely negative, suggesting that a definite curve, when present, represents an uncured condition, while a negative one might occasionally prove to be of little value in diagnosis or prognosis. Another patient (Case 13428), whose fluid showed a marked decrease in findings, had a very temporary improvement, following which he was worse than before.

Case 16137 presented a textbook picture of *tubercles* with typical Charcot joints, yet five different spinal fluids taken during the course of treatment were all negative with every routine test. One must consider here the possibility of previous treatment not obtained in the history, but even in that instance it proves quite conclusively that the spinal fluid findings do not always parallel the clinical progress of the disease in many instances.

Another case deserving of comment is Case 16942 in which, in the absence of any other demonstrable cause for the symptoms, syphilis was considered and treatment instituted. The curve was rather an indefinite one, pointing more to an irritative type (Zone III) than to a syphilitic type (Zone II). However, during the course of the treatment and development of the disease, the curve changed from 001333-3110 to 0000112211. Here, then, is a case proven at necropsy to be a neoplasm of the meninges and not syphilis, yet the colloidal gold curve diminished under specific treatment. One must consider here, of course, the possibility of syphilis in conjunction with the neoplasm, but the absence of a positive Wassermann or necropsy evidences practically eliminates such a condition.

Of the greatest significance of all is Case 15695, in which twenty-one spinal fluids were examined during a period of four years, while the patient was receiving treatment. She was admitted to the University Hospital on various occasions with well marked symptoms of

taboparesis, but each time improved markedly under treatment and was in this way enabled to be up and about as usual most of the time. But always on a "vacation" from treatment she had prompt recurrence of tabetic symptoms and mental disturbances. During these four years her spinal fluid has shown a typical parietic curve in spite of clinical improvement. Only once, and that comparatively early in the course, did the curve drop back into Zone II; the Nonne showed a great deal of fluctuation and the Wassermann was occasionally negative but the colloidal gold reaction remained constant.

Another point of interest that attracts one's attention on examination of the tables is the apparent "provocative" reaction, well illustrated by Cases 15803, 15857 and 15990. It is significant that the Wassermann also became positive under treatment. These cases prove quite conclusively a fact much disputed in the literature, namely, that a provocative reaction is possible in the spinal fluid as well as in the blood. Therefore, a patient suspected of having an incipient syphilitic infection of the central nervous system should not be pronounced free of the disease until an entirely negative spinal fluid has been obtained following one or several antisyphilitic treatments.

Occasionally one sees a spinal fluid giving a negative curve after treatment but very soon becoming positive again. This is very frequently (but not always) accompanied by a drop in the cell count and a negative Wassermann, as in Case 17811. Because of this fact, undue emphasis as to prognosis or regulation of the amount of therapy should not be put on one negative colloidal gold curve or a negative Wassermann, as only too often it is followed by later positive results, sometimes even more marked than formerly, if later spinal punctures be done. It also suggests the advisability of doing an occasional prophylactic spinal puncture on a patient who appears cured and has shown an entirely negative spinal fluid. While one admits that there is a marked lack of correlation between the colloidal gold curve and the severity or progress of the disease, one must grant that as long as a patient shows positive findings in his spinal fluid he cannot be considered cured.

In many of the cases in this series there was a definite intensification of the curve during treatment, and this can only be explained by suggesting the possibility of an increase in the extent or severity of the disease or by a temporary activation of the infection, causing an increase in the substances in the cerebrospinal fluid which precipitate the colloidal gold.

One very practical lesson to be learned from this study is the importance of a detailed history concerning former syphilitic treatment. A diagnostician seeing one of these patients for the first time might be led rather far afield if he placed much dependence on the spinal fluid

findings, all of which were negative or indefinite because of former treatment. For example, Case 19080 never showed a very pronounced colloidal gold curve although the other tests suggested tabes. In an attempt to find a reason for this, more detailed questioning revealed the fact that he had had fairly intensive treatment before being admitted to the hospital. Therefore, the colloidal gold reaction, which has been proved to be of primary importance in the diagnosis of affections of the central nervous system, may lose its significance and importance after the antisyphilitic treatment has been instituted. A marked curve, should it persist, will still be a valuable aid to diagnosis and to a less degree prognosis, but a low or negative curve may be only a detriment in the final consideration of the facts of the case.

It should here be stated that the treatment referred to is that of only the tertiary stage or that administered after the time which has elapsed until the usual appearance of the tertiary stage. Treatment given in the primary or secondary stages will either prevent the appearance of the lesions of the central nervous system or have no effect whatsoever on their tardy development. Much has been said in the current medical literature by various authors about the colloidal gold curve becoming atypical after treatment, although no detailed figures are given to show exactly what is meant by such a term. But those statements are not borne out in this series. Some curves decreased in intensity or disappeared altogether, but as long as they were present at all they remained in the same zone and were of the same type as when at their greatest intensity. In a very few instances, however, a curve in Zone I dropped back to Zone II after treatment, suggesting that that might be the order of disappearance; even then they were typical for Zone II. But in our series the majority of curves in Zone I resisted the effects of treatment.

The behavior of the Nonne, cell count and Wassermann reaction toward the antisyphilitic treatment is also of interest here. Of the thirty-five cases shown in the tables the Wassermann remained positive throughout in 15, or 43 per cent.; it became negative in 12, or 34.5 per cent.; in 4, or 11.5 per cent. it was negative throughout and in 6, or 17 per cent., it was negative at some time but again became positive and of these 6, 3 were "provocative."

The Nonne was uniformly positive in 16, or 45 per cent.; variable in 19, or 54 per cent., of which 6, or 17 per cent., became finally negative, and 8, or 23 per cent., were "provocative."

The cell count varied widely and apparently bore no relationship to the intensity or fluctuation of the colloidal gold curve or clinical progress or improvement of the disease. This variation in the cell

count has been noted by Mitchel, Darling and Newcomb,<sup>24</sup> who in two weeks made 300 counts on thirty-four patients with untreated syphilis, and found great variations in short intervals in every stage of the disease and no parallelism with the clinical symptoms. Solomon and Koefod,<sup>25</sup> in a similar study of cases after treatment, found a great variation in the number of cells, often in intervals of only a few days, and concluded that the cell count gives no definite information on duration, severity or prognosis of the disease and is of no value in differentiating between the different types of syphilitic infection of the central nervous system, which observations are borne out by this series. It may be noted here, however, that there was usually a decrease of cells under treatment, and they do not follow the colloidal gold curve or Wassermann in the provocative reactions.

When confronted by these apparently variable results, in seeking an explanation one naturally turns to the somewhat vague and variable theories of the cause of the action of the syphilitic spinal fluids on the colloidal gold and the resulting precipitation. One is first tempted into the field of theorizing by the possibility of the actual presence of the *Spirochaeta pallida* in the spinal fluid. We are accustomed to think of the late localization of this spirochete in the central nervous system as the actual cause of the various syphilitic infections of the brain or spinal cord—a condition which may be prevented by early and vigorous treatment. However, while admitting the possibility, one does not admit the probability of the spirochetes being the actual cause of colloidal gold curves. The difficulty with which the spirochetes are found in the fluid, the long persistence of the curve after the lesions have become chronic and inactive, and the lack of relationship between the curves and clinical symptoms or improvement do not support such a theory.

Second in consideration comes the possibility of the presence of antibodies being the causative factor, due to the intimate association of the spinal fluid and affected parts. We believe these antibodies to be the cause of the Wassermann reaction in the spinal fluid. However, the positive Wassermann and colloidal gold curves, while usually associated, frequently appear and disappear at entirely different times, occasionally one persisting long after the other. Therefore, one is justified in the assumption that they may be caused by entirely different substances.

A third possibility to be considered is that of changes, due to the disease, in the permeability of the choroid plexus, thereby causing a

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24. Mitchel, Darling and Newcomb: Observations on Spinal Fluid Cell Count in Untreated Cases of Cerebrospinal Syphilis, *J. Nerv. & Ment. Dis.* **41**:686, 1914.

25. Solomon and Koefod: Significance of Changes in Cellular Content of Cerebrospinal Fluid in Neurosyphilis, *Boston M. & S. J.* **173**:996, 1915.

change in the constituents of the spinal fluid. This has been thought to be true in meningitis where one has reason to believe that there is leakage of blood serum into the cerebrospinal fluid, a fact which is borne out by the ability to produce the same curve in Zone III by adding blood serum to the spinal fluid. One finds it difficult to believe, moreover, that the secretory apparatus could be so changed by the same organism as to produce products giving curves as different as those of paresis and tabes.

The last and most plausible possibility is that of definite changes or lesions produced in the central nervous system and giving off substances into the cerebrospinal fluid. In all probability advanced syphilitic lesions, like tuberculous lesions, are not cured or obliterated by treatment but merely rendered inactive or stationary. It is easy to believe, then, that these persisting lesions may continue to give off substances which may produce positive colloidal gold curves for a long period of time. This theory is strengthened by the fact that the earlier less marked cases show a colloidal gold curve soon returning to normal, while the later, well developed cases show a curve which resists all treatment. It is also possible that the type of this lesion may vary somewhat in individual cases which may mean that substances slightly different in amount or constituents may appear in various cases and produce colloidal gold curves which, while adhering to type, behave differently toward antisyphilitic treatment.

The elusive character or composition of such a substance has led to much conjecture and, as yet, incomplete experimental work. Weston,<sup>26</sup> thought that the reaction was caused by a globulin. Felton<sup>27</sup> considered it to be the effect of the relationship between the globulin and albumin—the former precipitating, the later protecting. Cruickshank<sup>28</sup> in a more recent article, after careful experimental work, found the colloidal gold curve to be caused by a change in the globulin and not merely increased globulin.

#### SUMMARY

1. The colloidal gold reaction shows a tendency to decrease under the influence of antisyphilitic treatment, but may remain unchanged or even increase in intensity.
2. The more pronounced the colloidal gold curve the less it is affected by treatment. On the other hand, the lower curves are more readily brought down to normal.

26. Weston: The Colloidal Gold Precipitating Substance in the Cerebrospinal Fluid in Paresis, *J. Med. Res.* **34**:107, 1916.

27. Felton: Cerebrospinal Fluid and the Colloidal Gold Test, *New York M. J.* **110**:1170, 1917.

28. Cruickshank: The Value and Mechanism of the Colloidal Gold Test, *Brit. J. Exper. Path.* **1**:107, 1920.

3. A positive colloidal gold curve may be of diagnostic value in cases having received previous treatment, but a negative reaction is of less significance.

4. A "provocative" reaction may appear in the spinal fluid as well as in the blood Wassermann as a result of the institution of treatment.

5. The colloidal gold reaction does not parallel or follow the clinical symptoms of the progression or regression of the disease.

6. If the colloidal gold curve changes after treatment, it increases or decreases in intensity and occasionally drops back into another zone, but is usually a symmetrical curve and does not become atypical.

7. The Nonne and Wassermann reactions tend to parallel the colloidal gold curve in its behavior to treatment and in the provocative reaction.

8. The cell count is increased only in spinal fluids from cases showing affection of the central nervous system, but even in such cases it is not always constant and bears very little relationship to the other routine tests or to clinical signs, improvement or provocative reactions.



# SINISTRALITY IN RELATION TO HIGH BLOOD PRESSURE AND DEFECTS OF SPEECH

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## INTRODUCTION

From the clinical point of view, left-handedness is usually regarded as an insignificant physical peculiarity. Various authors, it is true, point out that this affection may have a background of psychomotor symptoms, but such statements seem to have attracted very little attention. In 1870, Cooke<sup>1</sup> declared his belief that all left-handed persons are "more or less 'odd,'" and this is probably a fair expression of current opinion on the subject today. It does not appear to be generally known that in addition to a simple form, there are crossed forms of left-handedness or sinistrality. The simple, familiar form may reveal itself in an individual through some deviation from the right-handed conventions. On the other hand, the crossed forms are latent and unless they are sought for they escape observation. Left-eyedness, for example, is not uncommon in the right-handed and, conversely, right-eyedness is common in sinistrals. The etiology of these mixed types is obscure. Perhaps, in some instances they may be due to a compulsory change of handedness effected in early childhood. Few reports are available in the literature as to the relative numerical importance of the crossed forms, but they appear to be more prevalent than simple left-handedness.

The object of this paper is (1) to review the literature of the subject and (2) to present the results of an investigation of left-handedness in relation to high blood pressure and speech defects.

## REVIEW OF LITERATURE

In view of the fact that more or less exhaustive analyses of the literature of left-handedness are available in the papers of Beeley,<sup>2</sup> Smith<sup>3</sup> and others, it will suffice for the present purpose to consider previous contributions with especial reference to (a) heredity, (b) prevalence and (c) symptoms.

*Heredity.*—Bardeleben<sup>4</sup> carried out extensive osteologic studies on

1. Cooke, R. H.: Left-Handedness. *Lancet*, **2**:526, 1870.

2. Beeley, A. L.: Left-Handedness. *Am. J. Phys. Anthropol.*, **2**:389, 1919.

3. Smith, J. G.: A Brief Survey of Right-Handedness and Left-Handedness. *Pedagogical Sem.*, **24**:19, 1917.

4. Bardeleben, K.: Ueber bilaterale Asymmetrie beim Menschen und bei höheren Tieren. *Anat. Anz.* **34**: Ergänzungshft. 2, 1909.

the higher anthropoid apes by means of comparative measurements of the long bones of the extremities. His results prove that, as a rule, the bones of the right side are the longer. Mollison (cited by Bardeleben) found that righthandedness is characteristic of man, the orang and the gibbon. It is most pronounced in man, less marked in the orang, and still less in the gibbon. Bardeleben states that his own results and those of Mollison show unmistakably that right-handedness and left-handedness occurs among the primates, but that the available data are inconclusive in many respects and throw very little light either on a primitive source of left-handedness or on any determining factor, aside from the general one of heredity.

Ramaley,<sup>5</sup> from a careful analytical study of data derived from 610 parents and 1,130 children, concludes that left-handedness is a mendelian recessive, and that "the condition probably exists in about one-sixth of the population."

Lithgow<sup>6</sup> gives an account of a family in which the "eldest son for three generations at least has been left-handed."

*Prevalence.*—Biblical authority (Judges xx, 15-16) establishes the fact that the tribe of Benjamin, which numbered about 25,000 men capable of bearing arms, had 700 left-handed soldiers who were especially skillful with the sling. In that remote age, therefore, according to this evidence, less than 3 per cent. of the male population were sinistrals.

Modern statistics are probably more trustworthy. Schaefer,<sup>7</sup> Ballard<sup>8</sup> and Smith<sup>3</sup> found, respectively, 4.06, 4 and 4.5 per cent. of left-handedness from surveys of a combined total of 32,318 school children. Stier<sup>9</sup> noted 5.1 per cent. as the proportion among 5,000 army recruits. Both Ireland<sup>10</sup> and Smith<sup>3</sup> reported 11 per cent. of left-handedness from their investigations of imbecile and feeble-minded children. Smith<sup>3</sup> states that the proportion among 500 delinquents was 6 and 11 per cent., respectively, for boys and girls, whereas the proportion among 500 deaf was 4.5 per cent.

From the statistical data just given it is obvious that approximately 4 per cent. of normal people are left-handed.

Turning to the question as to the frequency of latent or crossed sinistrality, two reports are available in the literature. Ballard<sup>8</sup> tested

5. Ramaley, F.: Inheritance of Left-Handedness, *Am. Naturalist*, **47**:730, 1913.

6. Lithgow, R. A.: Left-Handedness, *Lancet*, **2**:660, 1870.

7. Schaefer, M.: Die Linkshänder in den Berliner Gemeindeschulen, *Berl. klin. Wehnschr.*, **1**:295, 1911.

8. Ballard, P. B.: Sinistrality and Speech, *J. Exper. Pedagogy*, **1**:298, 1911.

9. Stier, E.: Linkshändigkeit, besonders in der Armee, *Deutsch. med. Wehnschr.*, **35**:1587, 1909.

10. Ireland, W. W.: Notes on Left-Handedness, *Brain*, **3**:207, 1880.

fifty-one left-handed people with respect to the "fixing-eye" and found that 57 per cent. of them were right-eyed and 43 per cent. were left-eyed. Hartshorne<sup>11</sup> found nine left-eyed individuals among seventy-two right handed patients. Of three left-handed patients, he states that two proved to be right-eyed and one left-eyed.

*Symptoms.*—(a) Psychomotor: Stier<sup>9</sup> emphasizes the fact that enuresis is a common symptom among sinistrals.

Ballard<sup>8</sup> makes use of the term "dextro-sinistral" for an individual, naturally left-handed, who from early childhood has been trained to use the right hand, and he points out that many stammerers belong in this class. Stier<sup>9</sup> agrees with Ballard that speech disturbances are particularly common among the left-handed, and the observations of Hollis<sup>12</sup> are in accord with this view. The statement of Liepmann<sup>13</sup> that left hemiplegia in a sinistral is rarely accompanied by motor aphasia also is of interest in this connection.

(b) Visual: Wray<sup>14</sup> described two ocular tests of left-handedness in the following words: "It is common knowledge that though the vision is perfect in each eye and the refraction normal, nearly every person has a master-eye; this is determined by holding a ring at arm's length with both eyes open and covering an object a few yards away. A left-eyed person on shutting his left eye will find the ring too far to his left. If, on the other hand, he shuts his right eye he finds he is dead-on his object. . . ." Another point to which reference may be made is the almost invariably superior coordination of the right hand with the right eye. To show this, facing 6/24 of Snellen's type, point promptly at the middle letter with the index finger of the right hand and shut the left eye. If righthanded the pointing is accurate. Now by pointing with the left index finger in the same way it will be found the pointing is accurate if the experimenter is left-handed but inaccurate if he is right-handed."

Rosenbach,<sup>15</sup> Baudouin,<sup>16</sup> Enslin<sup>17</sup> and Griesbach<sup>18</sup> fully confirm Wray's findings.

11. Hartshorne, I.: Right-Handedness and Left-Handedness, Albany M Ann., **32**:338, 1911.

12. Hollis: Lopsided Generations, J. Anat. & Physiol., **9**:263, 1875.

13. Liepmann, H.: Ueber die wissenschaftlichen Grundlagen der sogenannten "Linkskultur," Deutsch. med. Wehnschr., **37**:1249, 1911.

14. Wray, C.: Right-Handedness and Left-Brainedness, Lancet, **1**:683 (March 7) 1903.

15. Rosenbach, O.: Ueber monokulare Vorheerschaft beim binokularen Sehen, Muench. med. Wehnschr. **2**:1290 (July 28) 1903.

16. Baudouin, M.: Droiture et Gaucherie oculaires, Gaz. méd. de Par, Series 13, **4**:353 (July 23) 1904.

17. Enslin: Kurze Mitteilung ueber ein Augensymptom bei Linkshändern, Munchen. med. Wehnschr., **57**:2242, 1910.

18. Griesbach, H.: Ueber Linkshändigkeit, Deutsch. med. Wehnschr., **45**: 1408 (Dec. 18) 1919.

The objective data which have been referred to in this outline of the literature seem definitely to prove: (1) that left-handedness is hereditary, and (2) that it strongly suggests a relative inferiority in the organization of the central nervous system. The evidence in support of the first point is thought to be conclusive. With regard to the second point, the relatively frequent occurrence of speech defects among the left-handed would seem to show that, in comparison with right-handed people, they find themselves at a disadvantage in the execution of finely coordinated movements. Moreover, sinistrality is exceptionally prevalent among the feeble-minded.

#### RESULTS OF PERSONAL INVESTIGATIONS

*Technic and Results.*—As a tentative theoretical basis for the work here reported, four general propositions were kept in view:

1. That left-handedness is hereditary.
2. That left-handedness implies a relative inferiority in the organization of the central nervous system.
3. That the etiology of high blood pressure is unknown.
4. That if high blood pressure may be construed as in any sense indicative of constitutional inferiority, or of stresses or maladaptation in the central nervous system, then, comparative blood pressure determinations in right-handed and left-handed individuals, about of the same age, might yield information of some value.

In order to secure practical data, blood pressure observations were made on 142 inmates of the San Francisco Home for the Aged. In this institution there are 733 ambulatory males whose ages range from 44 to 89 years. A majority of the men are over 60, and only five men under 50 were encountered in the course of this work. Ruling out those who were rendered unavailable for examination because of loss of vision in one or both eyes, posthemiplegic contractures and other lesions, approximately 600 men were included in the survey. All of these old people live under the same conditions of housing and food.

*Method of Testing.*—Each man was questioned as to his handedness and as to whether he had been a stammerer in childhood or had suffered from other defects of speech. During the interrogation it was borne in mind that left-handedness may be simple or crossed and so the queries were varied to suit individual cases. In this way sinistrals were found who prefer to employ the left hand only in certain activities, and one right-handed sinistral was found who stated that although he fires a gun from the right shoulder he takes aim with the left eye. Pure sinistrals, of course, make use of the left hand practically in every manipulation. They hold a knife, spoon or pen in the left hand, fire a gun from the left shoulder, and wield various implements with the left arm and hand.

The "master-eye" was determined in each individual by means of Wray's tests, and, as a rule, the results were definite and satisfactory. For confirmative evidence, however, I made use of a pointing test based on Ballard's "cigar-box" test. A wooden "pistol" with a barrel nine inches long was used. Each end of the barrel is furnished with a sight of fine steel wire one inch in height. The man to be tested is directed to seize the "pistol," hold it at arm's length and, with both eyes open, quickly point it at the observer and at the same time to bring the sights into line. If now the observer faces the "pistol" at a distance of twenty feet or more, it is at once apparent to him with which eye the man takes aim. The "fixing-eye" usually remains the same, irrespective of the hand in which the "pistol" is held.

Systolic blood pressure observations were made in the customary manner with Faught's instrument.

*Results.*—(a) Sinistrals: In the examination for handedness of about 600 men, forty-two sinistrals were found. These sinistrals include twenty-eight left-handed and fourteen right-handed individuals.

The visual tests led to an even division of the twenty-eight left-handed men, as 50 per cent. of them proved to be right-eyed and 50 per cent. left-eyed. On the other hand, the fourteen right-handed men were found to be left-eyed. In view of these findings, therefore, it became possible to subdivide the original forty-two sinistrals into three equal groups, designated as: Group 1, left-handed, left-eyed, pure sinistrals; Group 2, left-handed, right-eyed, crossed sinistrals, and Group 3, right-handed, left-eyed crossed sinistrals.

Although no record of the number was kept, it seems worth while to note the fact that fully one-half of the men in Groups 2 and 3 laid claim to ambidexterity.

Five men in Group 1 and two men in Group 2 gave a history of stammering. Group 3 was negative in this respect.

(b) Dextrals: For comparison with the sinistrals, blood pressure observations were made on 100 unselected, right-handed, right-eyed dextrals. The members of this group were secured from a large assemblage of the men, in the order in which they came forward for examination, and they are in every way representative of the general body of inmates at the Home. Each man was questioned as to his handedness and his eyes were examined in the manner already described. All men thus tested who proved to be both right-handed and right-eyed were accepted as dextrals and determinations of blood pressure were made forthwith.

Five men in the dextral group gave a history of stammering.

The general results obtained in the examinations of the four groups are brought together for comparison in Tables 1 and 2.

TABLE 1.—COMPARATIVE BLOOD PRESSURE DETERMINATIONS IN SINISTRALS, CROSSED SINISTRALS AND DEXTRALS

	Mean Age	Blood Pressure Values		
		Over 150 Mm., per Cent.	150 Mm. or Less, per Cent.	Mean Value, Mm.
Group 1: 14 pure sinistrals (left-handed, left-eyed men) .....	65.5	71.4	28.5	166.7
Group 2: 14 crossed-sinistrals (left-handed, right-eyed men) .....	68.2	85.7	14.2	182.1
Group 3: 14 crossed-sinistrals (right-handed, left-eyed men) .....	63.2	71.4	28.5	174.9
Group 4: 100 pure dextrals (right-handed, right-eyed men) .....	69.4	46.0	54.0	154.5

TABLE 2.—SPEECH DEFECTS IN SINISTRALS, CROSSED SINISTRALS AND DEXTRALS

	History of Stammering in Childhood, per Cent.
Group 1: pure sinistrals.....	35.7
Group 2: crossed sinistrals.....	14.2
Group 3: crossed sinistrals.....	0.0
Group 4: pure dextrals.....	5.0

## SUMMARY

A survey of approximately 600 men between the ages of 44 and 89 was made with a view to determine (1) the relation of left-handedness to high blood pressure and (2) the relation of left-handedness to defects of speech. The following results were obtained:

1. Forty-two sinistrals or 7 per cent. were found. Classified with reference to the dominant or "master-eye," these sinistrals form three groups, designated as:

Group 1, left-handed, left-eyed, pure sinistrals.

Group 2, left-handed, right-eyed, crossed sinistrals.

Group 3, right-handed, left-eyed, crossed sinistrals.

2. Compared with a group of 100 right-handed, right-eyed, pure dextrals, the mean blood pressure values observed in the sinistral groups were from 7.8 to 17.8 per cent. higher.

3. A mean value of 154.5 mm. was obtained for the dextral group. The mean value obtained for the crossed sinistrals of Group 2, was 182.1 mm.

4. In the three sinistral groups blood pressure values higher than 150 mm. were noted in from 71 to 85 per cent. of the men, as against 46 per cent. in the dextral group.

5. Five per cent. of the pure dextrals gave a history of stammering. The proportion in the group of pure sinistrals was 35.7 per cent.

## CONCLUSIONS

1. High arterial tension occurs more frequently in left-handed than in right-handed people.

2. In view of the evidence submitted that left-handedness is hereditary, and that it indicates a defective organization of the central nervous system, it is concluded that hereditary predisposition is a definite factor in the etiology of high blood pressure, and that high arterial tension is suggestive of constitutional inferiority.

3. As compared with dextrals, stammering occurs in sinistrals with a frequency from three to seven times greater.

## THE SIGNIFICANCE OF THE EMBOLIC GLOMERULAR LESIONS OF SUBACUTE STREPTOCOCCUS ENDOCARDITIS \*

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In a previous paper,<sup>1</sup> based on a study of the kidneys of twenty-three cases of subacute bacterial endocarditis due to the *Streptococcus anhemolyticus* (*Streptococcus viridans*), it was found that in twenty-three of the cases a distinctive pathologic lesion existed in the glomeruli. This pathologic picture had previously been described by Loehlein<sup>2</sup> in two cases of the disease. As a result of our more extensive study, we were inclined to believe that the lesion was specific for this disease.<sup>3</sup>

We were also able to demonstrate at that time that the lesions, as had been suspected by Loehlein, are due to small bacterial emboli which destroy one or more loops at some part of a glomerulus. Eventually, complete organization of this damaged segment takes place by invasion of fibroblasts from the periphery of Bowman's capsule.

The salient features of the lesion which serve to differentiate it from other types of glomerular disease are, first, the involvement of one or more loops of a variable number of glomeruli; second, the absence of any visible disease in the uninvolved glomeruli and in the uninvolved portions of affected glomeruli; and thirdly, the association in most of the bacterial cases of all stages of the glomerular process, often seen in a single microscopic section.

These characteristic embolic glomerular lesions usually involve only a small minority of the glomeruli. To date, a wealth of material has been accumulated, seventy-seven cases of subacute streptococcus endocarditis having come to necropsy at the Mount Sinai Hospital, and in only six were as many as from 60 to 90 per cent. of the glomeruli involved by the embolic process.

Because of the almost universal involvement of the glomeruli in these cases, the microscopic picture appeared at first glance not unlike

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\* From the Pathological Laboratory of the Mount Sinai Hospital. Work done during the tenure of the George Blumenthal, Jr., Fellowship in Pathology.

1. Baehr, G.: J. Exper. M. **15**:330, 1912; Am. J. M. Sc. **144**:327, 1912.

2. Loehlein: Med. Klin. **6**:375, 1910.

3. Since that time (1912) we have had occasion to modify this view slightly. One exception has since come under observation in which typical glomerular lesions were present, but no endocarditis. The case was not carefully studied during life, but was apparently some obscure infection complicated by a pericarditis. Autopsy revealed in addition to a dry pericarditis, multiple focal necroses in the liver and spleen, and glomerular lesions indistinguishable from those of subacute streptococcus endocarditis.



that of an acute or chronic glomerulonephritis. In fact, in nine other cases in this series which form the subject of another communication,<sup>4</sup> the typical glomerular lesions were obscured by a diffuse, practically universal glomerulotubular damage, an acute glomerulonephritis or its sequel, chronic diffuse nephritis. The present series of six cases differs radically from these, for on closer study and in accordance with the criteria just mentioned, it could readily be ascertained that the numerous glomerular lesions were all of the embolic type.

In four of these cases in which death occurred in the bacterial stage of the endocarditis, all stages of the glomerular lesions were to be seen, the same microscopic preparation furnishing examples ranging from the most recent to the completely organized stage of the process. Often a single glomerulus would show different stages of involvement in different portions. Occasional normal glomeruli were to be encountered, but these, according to the recent work of Fahr, would not exclude a true glomerulonephritis of focal distribution. Of more significance, however, was the fact that the uninvolved portions of damaged glomeruli remained perfectly normal.

In two other cases which terminated in death in what Libman<sup>5</sup> has described as the bacteria-free stage of the endocarditis, only healed glomerular lesions were present. But these were so typical that the possibility of the lesions being due to an antecedent glomerulonephritis could be excluded. In these cases, also, the uninvolved portions of damaged glomeruli remained perfectly normal.

The great numerical frequency of the glomerular lesions in the above six cases afforded an opportunity to ascertain the effect of such lesions upon the renal function. Clinical studies of this nature will subsequently be published in collaboration with Dr. E. Libman. For present purposes, it is sufficient to state that except for slight albuminuria and microscopic hematuria, none of these cases manifested any symptoms which might be construed as indicative of a serious disturbance in renal function.

In other words, even when almost all the glomeruli have been more or less damaged by this embolic process, the function of the kidney may be unaffected. The explanation is probably to be seen in the observation that, unlike in true glomerulonephritis, the uninvolved portions of the damaged glomeruli remain normal. Blood continues to circulate through these undamaged capillary loops, and this is apparently sufficient to maintain the normal glomerular functions.

Another effect of this preservation of a normal circulation through portions of most of the glomeruli is to be seen in the tubules in these

4. Bachr and Lande: *J. A. M. A.* **75**:789 (Sept. 18) 1920.

5. Libman: *Am. J. M. Sc.* **146**:625, 1913.

kidneys. Most of the blood supply to the tubules of the cortex must first pass through the glomerular capillaries. Damage to an entire glomerulus, which occurs so frequently in a true diffuse glomerulonephritis, interferes, therefore, with the circulation to the appropriate tubular labyrinth and so induces tubular destruction. On the other hand, damage limited sharply to a portion of a glomerulus apparently has no such deleterious effect on the tubular labyrinth in connection with it. Degeneration and atrophy of tubules with coincident replacement fibrosis in the interstitium which occurs diffusely throughout the kidney after a true glomerulonephritis, is seen here only in occasional isolated foci where a glomerulus happens to be destroyed completely by the embolic process.

In the light of the above observations, the development of symptoms of renal insufficiency in a patient who is suffering from a subacute streptococcus endocarditis is evidence of a diffuse acute glomerulonephritis, or its sequel, chronic diffuse nephritis. This has actually been my experience nine times in this series of seventy-seven cases and forms the subject of a previous report.<sup>4</sup> One can be reasonably certain that the intercurrent appearance of symptoms of renal insufficiency in a case of subacute streptococcus endocarditis is not to be ascribed to the embolic glomerular lesions.

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## TREATMENT IN BOTULISM \*

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AND

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Medical research during the past ten years has greatly advanced our knowledge of *Clostridium botulinum* (*Bacillus botulinus*) and of botulism. Recent occurrences of botulism in man and domestic animals throughout the United States, and particularly in California, have drawn attention to and greatly stimulated research in all phases of this disease. Until recently these researches were conducted mainly by investigators connected with the national government and state institutions. The National Canners Association is spending large sums of money investigating food poisoning with the object of improving canning methods and preventing further outbreaks of botulism.

E. C. Dickson<sup>1</sup> has energetically attacked the problems connected with the subject of botulism. He has established the common occurrence of botulism in the United States, the fact that toxin is found in preserved fruits and vegetables, the occurrence of two types of toxin in this country, as in Europe, the relation between *C. botulinum* and "limberneck" in chickens and the symptom complex.

G. S. Burke<sup>2</sup> has established the common occurrence of the organism in nature and the extreme heat resistance and heat inhibition of the spores, thus accounting for the occurrence of the organism and its toxins in preserved foods. She has also designated the two types of *C. botulinus* found in this country as types A and B.<sup>3</sup>

Robert Graham<sup>4</sup> and his co-workers have made extensive investigations and have definitely established the relation between *C. botulinum* and forage poisoning.

\* From the Department of Bacteriology and Experimental Pathology, Stanford University.

1. Dickson, F. C.: Botulism, Monograph No. 8 of the Rockefeller Institute for Medical Research, and subsequent papers.

2. Burke, G. S.: The Occurrence of *B. botulinus* in Nature, *J. Bacteriol.* **4**:541 (Sept.) 1919; The Affect of Heat on the Spores of *B. botulinus*, *J. A. M. A.* **72**:88 (Jan. 11) 1919.

3. Burke, G. S.: Notes on *B. botulinus*, *J. Bacteriol.* **4**:555 (Sept. 5) 1919.

4. Graham, Robert: Studies in Forage Poisoning, *Bulls.* 207 and 208, Kentucky Agricul. Exper. Station, and subsequent papers.

A number of others have verified and extended the results of these workers, so that at the present time we have a fairly satisfactory knowledge of *C. botulinum* and the symptoms produced by its toxins in man and domestic animals.

While our knowledge has been developing along these lines, there has been little or no advance toward a satisfactory treatment in botulism. The Europeans had already shown that an antitoxin could be produced and would neutralize the toxin in "in vitro" and to a limited extent in "in vivo" experiments. Kemper<sup>5</sup> was able to show that if antitoxin was injected twenty-four hours after the injection of a forty-eight hour fatal dose of toxin, a number of the animals could be saved. And Dickson and Howitt<sup>6</sup> have verified these findings and shown that when rabbits are fed the toxin in amounts sufficient to cause death in forty-eight hours, the injection of a homologous antitoxin in twenty-four hours will save the animals. No one has, so far as I am aware, fed toxic cultures of *C. botulinum* and then shown that the animals could be saved by the use of an antitoxin after the symptoms appear. This is the condition met with in general practice, and until it is shown that men or animals can be saved from fed lethal doses of toxic cultures of *C. botulinum* by the injection of antitoxin at or about the time that the symptoms appear, we must not look forward with any great expectations to the use of antitoxin in the treatment of botulism.

An examination of the literature offers no encouragement in so far as nonspecific treatment is concerned. We find that physicians have used a wide range of substances in treating cases of botulism. None of these men affirm that the treatment used materially altered or checked the course of the disease.

In viewing the problems presented by our present knowledge of the subject it seemed to us that future research in the treatment of botulism should proceed along four definite lines: (1) to determine the exact nature of the action of the toxin in the body; (2) to determine whether the toxin is extensively produced in the animal body and if produced, to develop some means of preventing its production; (3) to determine the amount of protection to be expected from the use of antitoxin if given at or about the time the symptoms appear; (4) the development of some preliminary treatment which will delay or prevent any further absorption of the toxin pending the arrival of the physician or the antitoxin.

We have no exact knowledge of the nature of the action of the toxin in the body. The result of the action is very evident in loss of

5. Kemper: Weitere Beiträge zur Lehre von der Fleischvergiftung. Das Antitoxin des Botulismus, Ztschr. f. Hyg. u. Infektionskrank 26:481, 1897.

6. Dickson and Howitt: Botulism. A Preliminary Report of a Study of the Antitoxins of *B. botulinus*, J. A. M. A. 74:718 (March, 13) 1920.

muscular control, death usually resulting from respiratory failure. It has not been determined whether the action of the toxin is central or terminal. The solution of this problem may give us a starting point for the development of some treatment of value.

It is generally stated in the literature that botulism is caused by the ingestion of preformed toxins. Orr<sup>7</sup> has taken issue with this statement and presents the results of some experiments which suggest that some cases of botulism may be due to an infection. This is important to the physician as well as to the canners. It is obvious that if we are dealing with an infection, the treatment must differ from what it should be if we are dealing only with the ingestion of preformed toxins. This question of infection will be discussed in detail later.

The experience recorded in the use of antitoxin in practical therapy is largely discouraging. There are several reasons for the apparent failure of the antitoxin treatment in botulism, the principal ones being that in most cases a heterologous antitoxin was used, and in all cases the treatment was commenced late in the course of the disease, usually several days after the symptoms appeared. Further experimental work should be done to determine just how effective the antitoxin treatment will be in all stages and conditions of botulism.

Since antitoxin is obtained only after delay, if obtained at all, it is essential that the attempt be made to develop some effective non-specific treatment. Most of the experimental work recorded in this paper was done in an effort to develop a treatment of this type. It was planned to make an exhaustive study of this phase of the subject but unfavorable conditions forced a termination of the work and this preliminary report is presented with the hope of stimulating others to carry on these researches to a definite termination.

An examination of case reports shows that the different treatments used have been designed to stimulate the patient, to prevent further absorption of the toxin and to neutralize the toxin by the use of antitoxin. No one has made any serious attempt to show that the organism or its toxins can be destroyed in the digestive tract. The results obtained from the treatments used are very discouraging. No one ventures to assert that the treatments used have altered the death rate. Dickson<sup>8</sup> recommends emesis, lavage, purgation with magnesium sulphate or castor oil, irrigation of the colon, giving water by rectum or by hypodermoclysis, strychnin, pilocarpin to counteract diminished secretions, cardiac and other stimulants as needed. Frost<sup>9</sup> recommends

7 Orr: *Abstr. Bacteriol.* 4:10 (Feb.) 1920.

8. Dickson: *Monograph No. 8*, Rockefeller Institute for Medical Research.

9. Frost: *Am. Med.*, February, 1915, p. 85.

the use of ipecac to stimulate glandular secretions in the intestines to check absorption. He also recommends rectal feeding, heroin, calomel, epinephrin, peptonized milk and whisky. Others have resorted to the use of digitalis, camphor, atropin, sodium phosphate, intravenous injections of salt solution, Glauber's salt, Epsom salt, olive oil, strophanthin, pituitary extract, gelsemium, colon enemas, stomach pump for evacuation and feeding, feeding through duodenal tube, and warm blankets for making the patient more comfortable. In a few cases the patient reported some temporary relief. Pilocarpin gives temporary relief from the accumulation of tenacious mucus in the pharynx. Pneumonia is frequently a complicating cause of death and should always be guarded against.

#### INFECTION VERSUS PREFORMED TOXINS

The possibility of botulism resulting from the ingestion of toxin-free organisms is discussed here in considerable detail because of its importance to the canning industry, to the epidemiologist, its bearing on the treatment of botulism and because the available data are not conclusive.

After considerable experimental work, von Ermengem<sup>10</sup> concluded that *C. botulinum* does not produce its toxins in the animal body. He fed washed bacilli and also injected them subcutaneously and intravenously without producing symptoms of botulism. He recovered the organism from the spleen and liver but could not demonstrate its presence in sections.

Thom, Edmondson and Giltner<sup>11</sup> attempted to determine whether *C. botulinum* spores freed from toxin by heating and by washing with salt solutions would produce toxin within the animal body. They found that if cultures containing spores were freed of toxin by heating to 80 C. for ten minutes and then were fed to or injected into animals no symptoms developed. If the organisms were washed seven times and injected into guinea-pigs or rabbits, the animals died, but if the cells were washed fourteen times the animals lived. In the heated cultures, the bacilli and their toxins were destroyed, leaving only the spores. In the washed cultures, the cells and spores remained, only the toxin being removed. The results obtained from washing the organisms fourteen times seem to indicate that the difference in results between heating and washing seven times is not due to the presence of more cells or to the presence of bacilli as well as spores and the produc-

10. Von Ermengem: Contributions à l'étude des intoxications alimentaires. Arch. pharmacodyn. 3:213 1897.

11. Thom, Edmondson and Giltner: J. A. M. A. 73:907 (Sept. 20) 1919.

tion of toxin in the body, but to the presence of preformed toxins which were not washed away. The organisms were recovered from the feces of the animals which were fed spores (freed from toxin either by heat or by washing), and from the liver and spleen of animals injected with cultures. These authors conclude that "colonization of the bacilli in the body has not been proved thus far, but the foregoing isolations from feces prove that the organism goes through the guinea-pig's body in from twenty-four to forty-eight hours with undiminished virulence."

Armstrong, Story and Scott<sup>12</sup> repeated with some modifications the experiments of Thom, Edmondson and Giltner. They injected subcutaneously in guinea-pigs 300,000,000 bacilli, previously heated to 80 C. for thirty minutes. No symptoms developed. The bacilli undoubtedly were killed by the heat, and they do not estimate the number of spores present. Cultures following the heating indicated the presence of viable organisms. Guinea-pigs injected subcutaneously with 300,000,000 bacilli, previously washed twelve and fourteen times, respectively, died. A guinea-pig injected subcutaneously with 120,000,000 organisms which had been washed on a Berkefeld filter by passing 800 c.c. of saline solution through the filter died in four days. Guinea-pigs receiving 12,000,000 similar organisms remained well. A guinea-pig force fed 1,200,000,000 washed organisms died in seventy hours, while another animal given the organisms on grass and meal showed no symptoms. The authors apparently favor the view that it is difficult to wash the toxin from the bacilli and that the death of the guinea-pigs in their experiments was due to this failure rather than that the toxin was produced in the animal bodies. It seems to us that a third explanation is possible, i. e., that there is some intracellular toxin and this is liberated on the death and lysis of the bacilli. This may explain the results obtained in the experiments of Armstrong, Story and Scott, in which a guinea-pig receiving 120,000,000 or more washed bacilli died, while a guinea-pig receiving 12,000,000 similar organisms lived. However, it does not explain the results obtained by Thom, Edmondson and Giltner in which it was shown that a guinea-pig injected with bacilli washed seven times died, while a guinea-pig injected with the same number of bacilli washed fourteen times lived, unless we assume that continued washing extracts the toxin from the interior of the cells.

Orr<sup>13</sup> has recently recorded some experiments which differ from those already described. All the details of Orr's work are not yet available so that we cannot carefully compare his experiments with the work of others. Orr found that guinea-pigs receiving large numbers of

12. Armstrong, Story and Scott: *Pub. Health Rep.* **74**:2894 (Dec. 19) 1919.

13. Orr: *Abstr. Bacteriol.* **4**:10 (Feb.) 1920.

toxin free spores (heated to 80 C. for thirty minutes) either per os or subcutaneously, usually died in from two to four days. Control pigs receiving antitoxin lived. The organisms were recovered from the spleen and liver in many of the animals, and in one case botulinus toxin was demonstrated in the brain tissue by mouse inoculation. Orr concludes that some cases of botulism may be due to a true infection.

Orr's results differ from those of other workers and suggest that *C. botulinum* may develop and produce its toxins in the animal body. Whether it ever happens that toxin-free organisms are ingested in sufficient numbers to cause botulism is of more interest to the canners and epidemiologists than to the physician. What is of particular interest to the medical profession from the standpoint of treatment is whether the toxin is being produced in the patient after the symptoms appear. The first case requires that the organisms grow and produce toxin in a normal digestive tract; the second, that the organisms grow and produce toxin after peristalsis has been reduced or has ceased. If the first occurs, the second naturally follows, but not the reverse. The production of toxin in the human body, if it occurs at all, may occur only after the ingestion of preformed toxin. Experiments were begun to determine this point, but were not carried far enough to warrant reporting.

If botulism ever occurs in human beings following the ingestion of toxin-free bacilli or spores we should find evidence of it. (1) There should be recorded outbreaks of botulism without a history of spoiled food and (2) without a history of preserved food. (3) It should be possible to demonstrate experimentally an infection following the ingestion of toxin-free organisms. (4) There should be more cases of botulism, unless an extremely large number of organisms are necessary for the development of an infection. (5) Outbreaks of botulism should follow the eating of thoroughly cooked spoiled preserved foods.

#### I. THERE SHOULD BE RECORDED OUTBREAKS OF BOTULISM WITHOUT A HISTORY OF SPOILED FOOD

We cannot say that all outbreaks of botulism have been due to spoiled food. Nor can we say that there have been outbreaks of botulism without a history of spoiled food. The records of the early outbreaks are incomplete. In all recent, thoroughly investigated outbreaks it has been stated by some of those involved in each outbreak that the food under suspicion tasted a little "off"; others have stated that they noticed nothing peculiar about the food, and, in fact, liked it.

This criterion is of little value in helping us to reach a decision because of the fact that spoiled foods are not readily separated from



unspoiled foods, and that people are careless about discarding food that is slightly suspicious. The standards by which spoilage in food is judged differ with different people, and food containing a naturally strong or peculiar odor may be in the early stages of botulinus spoilage and contain toxin sufficiently strong to cause disease without the taste, smell or appearance being sufficiently altered to attract the attention of the average individual. Also when mild flavored, slightly decomposed food containing toxin is mixed with other foods the detection of any unusual condition of the food is difficult. Such foods would be classed as unspoiled by some individuals. Some scientific observers believe that botulinus spoilage in preserved foods can always be detected by a careful examination, others are doubtful. The subject of botulism has received such publicity that we may expect to see a reduction in the number of outbreaks in families where the housewife oversees the cooking, but in many institutions and public eating houses the ignorant cook still rules. For this reason, the evidence given as to the condition of the suspected food will in some cases be inconclusive and of little value in determining whether there are ever any outbreaks of botulism without a history of spoiled food.

## 2. THERE SHOULD BE RECORDED OUTBREAKS OF BOTULISM WITHOUT A HISTORY OF PRESERVED FOOD

It has been shown that *C. botulinum* occurs in nature on fresh fruits and vegetables. It follows that many of us ingest the organisms without ill effects. If the ingestion of small numbers of toxin-free spores causes an infection, we should have cases of botulism without a history of preserved food having been eaten a short time before the onset of the symptoms. The epidemiologic data concerning most of the outbreaks of botulism are not sufficiently detailed to prove without question that a certain food caused the outbreak. But the fragmentary evidence that we have indicates that all outbreaks of botulism have been preceded by the eating of preserved food. It has not been shown in the early outbreaks of botulism that these preserved foods contained the toxin or the organism of *C. botulinum*. However, in all recent thoroughly investigated outbreaks it has been shown that the preserved foods eaten, if any remained for investigation, contained *C. botulinum* or its toxin. Therefore, we feel justified in believing that botulism in man does not follow the ingestion of toxin-free spores, particularly in small numbers. We have no evidence that large numbers of toxin-free spores are ever ingested, except in cooked spoiled food. And the destruction of the toxin in spoiled foods by thorough boiling for a few minutes does not destroy the spores but does appear to prevent botulism.

3. IT SHOULD BE POSSIBLE TO DEMONSTRATE EXPERIMENTALLY  
AN INFECTION FOLLOWING THE INGESTION OF  
TOXIN-FREE ORGANISMS

We have already cited the results obtained by von Ermengem, Thom, Edmondson and Giltner, and Armstrong, Story and Scott, in which infections did not follow the feeding and injecting of toxin-free organisms, and of Orr, who was able to demonstrate the presence of toxin in the animal body following the feeding of toxin-free spores. The conflicting results obtained by these workers have not been explained, and we must await repeated experiments for knowledge of the determining factors. Orr's results suggest that an infection may sometimes follow the ingestion of large numbers of toxin-free spores.

THERE SHOULD BE MORE CASES OF BOTULISM UNLESS AN EXTREMELY  
LARGE NUMBER OF ORGANISMS ARE NECESSARY FOR  
THE DEVELOPMENT OF AN INFECTION

As has already been stated, the organisms are fairly common in nature, and many of us ingest them without the development of an infection. That there are not more cases of botulism indicates that a few toxin-free organisms will not start an infection in a normal individual. The experimental evidence shows that an infection following the ingestion or injection of toxin-free spores does not occur unless very large doses are given. We cannot conceive of any condition under which a very large number of toxin-producing organisms of *C. botulinum* would be ingested, except in the eating of heated preserved foods. Orr has reported strains of *C. botulinum* as having lost the power of toxin production. Such strains growing in preserved foods might afford an opportunity for the ingestion of toxin-free organisms. Since the virulence of the organism depends partly on toxin production, it is a question whether such strains, even if taken in large numbers, would regain the power of toxin production and cause an infection.

The statistical and experimental evidence indicates that botulism does not follow the ingestion of small numbers of toxin-free organisms. Whether toxin-free organisms ever occur in preserved foods, heated or unheated, in sufficiently large numbers to cause an infection in man is doubtful.

THERE SHOULD BE CASES OF BOTULISM FOLLOWING THE EATING OF  
THOROUGHLY COOKED SPOILED PRESERVED FOODS

No cases of botulism are recorded in this country as following the eating of thoroughly cooked food. We assume that much spoiled food has been cooked and eaten. Outbreaks are reported in which the eating of uncooked spoiled food caused botulism and the eating of portions

of the same food after cooking caused no symptoms. This is not entirely conclusive since occasionally a person eating the uncooked food also escapes illness. At least seven individuals have been reported as having eaten of food causing botulism in others without becoming ill.

Since there are no recorded outbreaks of botulism in this country following the eating of cooked spoiled food, and since the spores are highly resistant to heat, we believe it reasonable to assume that large numbers of spores have been eaten without causing symptoms of botulism.

It is to be expected, however, that cases of botulism will occasionally occur from the eating of insufficiently cooked or heated spoiled food. A little warming will not destroy all the toxin. Spoiled food containing considerable gas appears to be boiling at temperatures of from 70 to 80 C. Bubbles may rise to the surface for at least five minutes before the true boiling point is reached. The statement is found in the literature that boiling spoiled food for five minutes makes it safe to eat. Thom, Edmondson and Giltner reported that at a temperature of 75 C. no appreciable time is required for the destruction of the toxin in a filtrate. Orr records destruction of the toxin in two minutes at 80 C. Others have reported similar findings. Boiling ordinary canned fruits and vegetables for five minutes should raise the temperature in the fruits or vegetables up to or above 75 C. and cause the destruction of all the toxin present, unless the toxin in the fruit tissues and juices is more resistant to heat than toxin in filtrates. In foods in which there is so much gas present that boiling appears to begin at 75 C., an exposure to this temperature for five minutes may not destroy all the toxin in the interior of the food, and botulism may result from the eating of such cooked food and be caused by the undestroyed toxin.

*Experiment to determine the effect of heat on the disease producing power of the juice from a can of spoiled beans containing C. botulinum and its toxin.*—The following experiments throw some light on the questions here involved and they simulate as nearly as possible conditions found in home cooking. The beans used were canned six months previously and contained a strong Type A toxin. The beans were badly spoiled and contained gas. One half pint of the beans with the juice was placed in a large beaker and brought to a boil. At intervals some of the juice was withdrawn and injected subcutaneously into guinea-pigs. The results obtained (Table 1) indicate that:

1. Spoiled foods containing gas may appear to be boiling for several minutes before the true boiling point is reached.
2. The destruction of the toxin in the bean juice may require considerable more exposure to heat than is recorded for toxin in filtrates.

3. Under the conditions of this experiment the disease-producing power of the bean juice was not wholly destroyed after exposure for nine minutes to temperatures changing from 70 C. to 100 C. or after exposure to boiling for four minutes.

4. The disease producing power of a can of spoiled beans containing *C. botulinum* and its toxin may be destroyed by a temperature that does not destroy the spores of *C. botulinum*.

5. Spoiled canned foods may appear to have boiled seven minutes and still be unsafe to eat.

TABLE 1.—EFFECT OF HEAT ON THE DISEASE PRODUCING POWER OF JUICE FROM SPOILED BEANS CONTAINING *C. BOTULINUM* AND ITS TOXIN

Time Minutes	Temperature and Appearance of Beans	Guinea- Pig	Weight, Gm.	Amount Injected, C.c.	Results
	Unbeated.....	1	250	1	Dead 18 hours
	Unbeated.....	2	250	0.01	Dead 18 hours
0	Burner lighted				
4	70 C. bubbles beginning to rise				
6	82 C. active bubbling, resembling boiling				
7	92 C. active bubbling, resembling boiling.....	3	250	1	Dead 96 hours
8	98 C. large bubbles				
9	100 C. true boiling.....	4	250	1	Dead 96 hours
13	100 C. true boiling.....	5	250	1	Dead 17 days
19	100 C. true boiling.....	6	250	1	Lived

In this experiment no effort was made to determine whether the animals died from the effects of the toxin formed in the can of beans or in the animal body. A filtrate of the heated juice was not tested for toxin and the presence of spores was not determined. However, one fact of importance is evident. The disease producing power of a can of spoiled beans may be destroyed by a temperature that does not destroy the spores of *C. botulinum*. Exposure of the spores to a temperature of 100 C. for ten minutes does not prevent their development and toxin production in culture mediums. If the spores ever cause an infection, heat may affect their virulence for the animal body. This experiment cannot serve as the basis for any definite conclusions as regards the infection theory because of the three unknown and uncontrolled factors: (1) the effect of heat on the toxin in bean juice; (2) the effect of heat on the vegetative forms in bean juice; (3) the presence of spores and the effect of heat on the virulence of the spores of *C. botulinum*. The results indicate, however, that we may expect to have outbreaks of botulism following the eating of poorly cooked spoiled food.

The results of this experiment indicate that spoiled food to be safe to eat must be boiled for at least fifteen minutes. And if the spores of *C. botulinum* are found to cause an infection in man, a much greater exposure to heat may be required. Boiling for four hours does not destroy all the spores of *C. botulinum*.

*Experiment to determine the effect of boiling on the disease producing power of the juice from a can of spoiled beans containing C. botulinum and its toxin when oil stratified.*—About 100 c.c. of the beans and juice used in the preceding experiment were placed in a beaker, oil stratified, and exposed to heat at 100 C. The results obtained (Table 2) were similar to those of the preceding experiment, except that the disease producing power of the bean juice resisted the effects of the heat for a longer period of time. Guinea-pigs receiving 1 c.c. of the bean juice, exposed to 100 C. for ten minutes, died.

TABLE 2.—EFFECT OF TEMPERATURE OF 100 C. ON THE DISEASE PRODUCING POWER OF JUICE FROM SPOILED BEANS CONTAINING C. BOTULINUM AND ITS TOXIN WHEN OIL STRATIFIED

Time, Minutes	Temperature	Amount of Juice Injected, C.c. Guinea-Pig		Weight, Gm.	Result
		1	1		
	Unheated	1	1	250	Dead, 18 hours
	Unheated	0.01	2	250	Dead, 18 hours
0	Burner lighted				
6½	100 C.				
11½	100 C.	1	2	250	Dead, 96 hours
16½	100 C.	1	4	250	Dead, 96 hours
21½	100 C.	1	5	250	Lived
26½	100 C.	1	6	250	Lived

*Experiment to determine the effect of a temperature of 80 C. on the disease producing power of a can of spoiled beans, containing C. botulinum and its toxin, when oil stratified in a test tube and placed in a water bath.*—About 15 c.c. of the beans and juice used in the preceding experiments were placed in a test tube and oil stratified. This test tube was then placed in a water bath and kept at 80 C. No record was taken of the temperature in the test tube. Some of the bean juice

TABLE 3.—EFFECT OF TEMPERATURE OF 80 C. ON THE DISEASE PRODUCING POWER OF JUICE FROM SPOILED BEANS CONTAINING C. BOTULINUM AND ITS TOXINS WHEN OIL STRATIFIED IN A TEST TUBE AND PLACED IN A WATER BATH

Time, Minutes	Temperature	Amount of Juice Injected, C.c. Guinea-Pig		Weight, Gm.	Result
		1	1		
	Unheated	1	1	250	Dead, 18 hours
	Unheated	0.01	2	250	Dead, 18 hours
0	Test tube containing				
	beans placed in water bath				
11	80 C.	1	2	250	Dead, 72 hours
30	80 C.	1	4	250	Dead, 72 hours
61	80 C.	1	5	250	Dead, 72 hours

was taken from the test tube at intervals and injected into guinea-pigs. The results obtained (Table 3) indicate that under the conditions of this test, which largely resembles the conditions surrounding beans in the middle of a kettle placed on the stove to warm, the disease producing power of the bean juice was not destroyed after an exposure to a temperature of 80 C. for one hour. This suggests that the casual warming of spoiled foods to a temperature of 80 C., even over an

extended period of time may not make them safe to eat. Since such foods may appear to be boiling, it is evident that we may expect to have cases of botulism following the eating of so-called boiled foods. The epidemiologist must bear these facts in mind in investigating outbreaks of botulism.

#### INFECTION FOLLOWING THE INGESTION OF THE TOXIN AND THE ORGANISMS

While it is of great importance to the epidemiologist to know whether botulism ever follows the ingestion of toxin-free organisms, it is of equal importance to the physician to know whether an infection ever occurs following the ingestion of the toxin and the organisms. If botulism ever occurs following the ingestion of toxin-free spores, we may be justified in assuming that an infection may occur following the ingestion of both the toxin and the spores, particularly after the symptoms appear. In the latter case, conditions for the development of *C. botulinum* are presumably more favorable than in the normal digestive tract.

If an infection ever occurs this may account for relapses that sometimes follow an improvement in the condition of the patient. It sometimes happens that a patient shows considerable improvement and then suffers a relapse and dies. This may be accounted for on the basis of a required incubation period, the first symptoms being due to the ingested toxin and the relapse due to toxins produced in the body. Stiles,<sup>14</sup> in recording his own case states that he had a serious relapse after partially recovering from the first attack. Others have reported similar experiences.

If an infection occurs, i. e., production of toxin in the digestive tract or elsewhere in the animal body, following the ingestion of the toxin and the organisms of *C. botulinum* the following postulates should hold true.

1. There should be, within certain limits, no relation between the amount of infected food eaten and the severity of the symptoms. If infection does not occur then there should be a definite relation between the amount of food eaten and the severity of the symptoms. (Individual variations in resistance, effects of other foods eaten and the even distribution of the toxin in the food are modifying factors that must be taken into consideration.)

Armstrong, Story and Scott,<sup>15</sup> in investigating the Canton, Ohio, outbreak found a "remarkable correspondence between the amount

14. Stiles: J. A. M. A. **61**:2301 (Dec. 27) 1913.

15. Armstrong, Story and Scott: Pub. Health Rep. **34**:2877 (Dec.) 1919.

eaten and the severity of the illness." Those eating less of the poisonous food obtained less toxin and also a smaller number of organisms but "had the bacilli swallowed with the olives been capable of growing and producing toxin in the alimentary tract it seems that some of the people who ate small amounts but were little affected would have developed serious symptoms." They estimated that one olive contained several million bacilli and conclude that "a bite of olive containing this number of viable organisms, if capable of multiplying and forming toxin in the alimentary tract, would have caused serious infections." However, this does not show that an infection may not occur following the ingestion of large numbers of organisms and after paralysis has set in.

2. It should be possible to demonstrate the infection experimentally since the M. L. D. (minimum lethal dose) of the filtrate should be less than the M. L. D. of the culture.

Any difference in toxicity between filtrate and culture should be due to the organisms present in the culture unless the process of filtering eliminates some of the toxin as well as the organisms. Emerson and Collins<sup>16</sup> report that olive juice from spoiled olives "filtered through a Berkefeld filter was found to be slightly less toxic than the unfiltered juice." We await further experimental evidence of a similar nature.

3. If infection occurs in the body outside of the digestive tract it should be possible to detect the organisms in sectioned material. *C. botulinum* has been recovered at necropsy from the liver and spleen of both human and laboratory animals dead of botulism. If the organisms are able to multiply and start an infection in the spleen and other organs it should be possible to demonstrate their presence in sectioned material. All attempts to demonstrate the organism in microscopic sections of organs of animals dead of botulism have been unsuccessful.

#### CONCLUSION

The major evidence as we have presented it here favors the view that botulism in man very rarely, if ever, occurs following the ingestion of toxin-free organisms. The available evidence is too inconclusive to form the basis for any definite conclusions. Many of the facts presented can be explained in more than one way. Our own belief is that infection in human beings following the ingestion of toxin-free organisms never occurs. We are inclined to believe that the organism does produce toxin in the alimentary tract following the ingestion of preformed toxins and after paralysis has set in. Treatment

16. Emerson and Collins: J. Lab. & Clin. Med. 5:559 (June) 1920.

of the digestive tract should be designed to neutralize and wash out the toxin and inhibit or destroy the organisms.<sup>17</sup>

#### IMMUNE SERUM TREATMENT

Workers in Europe and in this country have shown that repeated injections of sublethal doses of *C. botulinum* toxin in various animals will stimulate the production of specific antitoxins. Experiments have shown that the antitoxin will neutralize the toxin in "in vitro" experiments and in "in vivo" if the antitoxin is injected before the toxin, or after the toxin if the injection is made before the system is fatally damaged. Since there are at least two immunologically distinct types of *C. botulinum*, it is necessary to use a polyvalent immune serum unless the type of toxin is known.

The extent to which antitoxin is effective in preventing death when injected some time after the toxin has been taken into the body has not been established definitely. Kempner<sup>20</sup> has shown that if antitoxin is injected twenty-four hours after a forty-eight hour fatal dose of

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17. After the present article was sent to press our attention was called to an article by Edmondson, Giltner and Thom (The Possible Pathogenicity of *Bacillus Botulinus*, Arch. Int. Med. 26:357 [Sept.] 1920), in which they discuss experiments the results of which agree with those of Orr. In referring to their experiments they state that, "They show that occasionally guinea-pigs will develop the specific disease and die when fed or injected with large doses of the spores freed from toxin in routine manner," i. e., by washing or heat or both. The authors contemplate experiments to determine whether the toxin causing the disease is present in the spores or bacilli when ingested or injected and protected from heat by the spore wall and released upon dissolution of the spore wall or is actually produced in the body after the spores germinate. One of the strains used caused death more consistently than the other. The feeding or injection of large numbers of organisms of the most virulent strain was not always fatal. One of the body defenses against anaerobe infection consists of the amount of oxygen in blood and tissue fluids. The injection of toxin free spores either subcutaneously or intravenously, may lead to a local lowering of the oxygen tension and necrosis making conditions favorable for the development of anaerobes. What factor this plays in experimental botulism remains to be determined. *C. botulinum* has not been recorded from war wounds. The experimental data suggests that it may occasionally occur in wounds and thus account for the failure of the patient to respond to tetanus and other common antitoxin treatment. The paper of Bullock and Cramer<sup>18</sup> suggests that the toxin free spores of tetanus are no more infectious than those of *C. botulinum*. The main problem from the standpoint of treatment is to determine whether there are outbreaks of botulism in man following the ingestion of toxin free spores and if such do occur whether the symptoms are typical or atypical as has been suggested by Shippen<sup>19</sup> and therefore leading to a wrong diagnosis.

18. Bullock and Cramer: A New Factor in the Mechanism of Bacterial Infection, Proc. Roy. Soc. London, Series B 90:513, 1920.

19. Shippen: Arch. Int. Med. 23:346 (March) 1919.

20. Kempner: Weiterer Beitrag zur Lehre von der Fleischvergiftung. Das Antitoxin des Botulismus, Ztschr. f. Hyg. u. Infektionskrankh. 26:481, 1897.



toxin many of the animals will live. Dickson and Howitt<sup>6</sup> verified Kempner's findings to the extent of showing that if the antitoxin is injected subcutaneously within twenty-four hours after a forty-eight hour fatal dose of toxin has been ingested the animals will live. This means that when small doses of toxin are fed, twenty-four hours is not sufficient time for the toxin to be absorbed and cause fatal injury to the animal. Antitoxin must be used before the nervous system has been injured fatally. The time required for this depends upon the amount of toxin ingested or injected. If large amounts of toxin are used an animal may be injured fatally by the time the first symptoms appear.

The problem the practitioner has to face during an outbreak is to save the patients showing symptoms and also those who have eaten the poisonous food but have not yet shown symptoms. No one has, so far as we are aware, shown experimentally that an animal can be saved from lethal doses of toxin by the injection of antitoxin after the symptoms appear. And no one has attempted to show how many hours before the symptoms appear the injection of antitoxin will protect. The experiments of Kempner and of Dickson show that an animal can be saved from a forty-eight hour fatal dose of toxin by the injection of antitoxin twenty-four hours before death would occur if the antitoxin was not injected. They do not indicate how many hours this would be before the symptoms appeared. Dickson injected the antitoxin subcutaneously. It might have been possible to protect his animals by later injections if these had been made intravenously.

The available statistical data of the various outbreaks in this country show a death rate of 90 per cent. among those first showing symptoms, and a death rate of 60 per cent. among those last showing symptoms. Frequently, two or three days will elapse between the appearance of symptoms in the first patient and the last patient to come down in an outbreak of botulism. Sixty per cent. of the latter die. The experimental evidence gives us reason to believe that some of these victims could have been saved by the injection of antitoxin if the injections had been begun as soon as the first patient showed symptoms.

The following experiments were designed to determine the extent of the protection afforded by antitoxin if injected after the symptoms appear. In order to approach the conditions found in general practice toxic cultures instead of toxic filtrates were used.

*Experiment to determine whether rabbits can be protected from lethal doses of toxic cultures of C. botulinum by the injection of antitoxin as soon as the symptoms appear.*—Each rabbit was force fed 6 c.c. of a ten day meat culture of *C. botulinum* Type B. Antitoxin was injected both subcutaneously and intravenously seventeen hours later.

At this time two of the rabbits were dead, one was practically dead and three showed slight symptoms of prostration. Two of the rabbits receiving antitoxin lived. Since these rabbits received about 2 minimum lethal doses of toxin and were showing the first symptoms of botulism, there is no question that they would have died without the injections of antitoxin. The results obtained (Table 4) indicate that some rabbits can be saved from the forced feeding of a lethal amount of a toxic culture of *C. botulinum* by the injections of antitoxin as soon as the symptoms appear. It is probable that a larger percentage of rabbits can be saved by the injection of antitoxin after the symptoms appear if a smaller amount of toxin is fed.

TABLE 4.—RESULTS OF AN EXPERIMENT TO DETERMINE WHETHER RABBITS CAN BE SAVED FROM LETHAL DOSES OF TOXIC CULTURES OF *C. BOTULINUM* WHEN FORCE FED BY INJECTION OF ANTITOXIN AS SOON AS SYMPTOMS APPEAR

Rabbit	Weight, Gm.	Amount of Culture	Interval Before Injection of Antitoxin	Results
1	1,750	6 c.c. per os	.....	Dead, 16 hours
2	2,700	6 c.c. per os	.....	Dead, 16 hours
3	2,850	6 c.c. per os	.....	Dead, 17 hours
4	1,925	6 c.c. per os	17 hours	Lived
5	2,115	6 c.c. per os	17 hours	Lived
6	2,750	6 c.c. per os	17 hours	Dead, 23 hours

The experiment was repeated with the exception that the injection of the antitoxin was delayed until the symptoms were more advanced.

*Experiment to determine whether rabbits can be saved from lethal doses of toxic cultures of C. botulinum by the injection of antitoxin after the symptoms are well advanced.*—Each rabbit was force fed 6 c.c. of the meat culture used in the preceding experiment. The injections of antitoxin were begun twenty-one hours after the feeding of the toxic cultures and were made subcutaneously and intravenously. At this time three of the rabbits were dead and the three receiving antitoxin were prostrated. All the rabbits receiving antitoxin died. One of these lived for sixty hours, but it cannot be certain that this was due to the action of the antitoxin, as rabbits show considerable variation in their resistance to the toxin when force fed. The results obtained (Table 5) indicate that rabbits cannot be saved from 2 M. L. D., force fed, of a toxic culture of *C. botulinum* by the injection of antitoxin after the symptoms are well advanced and the rabbits show evident signs of prostration.

Botulinus antitoxin has been used in a number of outbreaks of botulism with inconclusive results. Dickson<sup>21</sup> was the first in this country to use antitoxin as a therapeutic agent in cases of botulism.

21. Dickson: Arch. Int. Med. 22:483 (Oct.) 1918.

He used a Type A and B antitoxin and both patients recovered. The antitoxin was not injected until five days after the symptoms appeared, and he doubts whether it affected the course of the disease.

McCaskey<sup>22</sup> injected antitoxin in treating three patients in the Decatur outbreak and believed it to be the determining factor in the recovery of two of the patients. The third patient was almost dead at the time the antitoxin was administered. The antitoxin was not given until several days after the symptoms appeared.

Ransom<sup>23</sup> reports the use of antitoxin in the Clinton prison outbreak with beneficial results though given late in the course of the disease.

Randell,<sup>24</sup> Jennings, Haass and Jennings,<sup>25</sup> Armstrong, Story and Scott, and Sisco<sup>26</sup> report the use of antitoxin in treating patients suffering with botulism. No improvement in the condition of the patients was attributed to the use of antitoxin.

TABLE 5.—RESULTS OF AN EXPERIMENT TO DETERMINE WHETHER RABBITS CAN BE SAVED FROM LETHAL DOSES OF TOXIC CULTURES OF *C. BOTULINUM* WHEN FORCE FED BY INJECTION OF ANTITOXIN AFTER SYMPTOMS ARE WELL ADVANCED

Rabbit	Weight	Amount of Culture	Interval Before Injection of Antitoxin	Results
1	1,750	6 c.c. per os	.....	Dead, 21 hours
2	1,950	6 c.c. per os	.....	Dead, 18 hours
3	2,100	6 c.c. per os	.....	Dead, 12 hours
4	2,000	6 c.c. per os	21 hours	Dead, 24 hours
5	1,900	6 c.c. per os	21 hours	Dead, 60 hours
6	2,100	6 c.c. per os	21 hours	Dead, 36 hours

In all cases in which antitoxin has been used in the treatment of botulism, the antitoxin has been given late in the course of the disease, sometimes in small amounts, or was of the heterologous type. Under such conditions we could not expect to get encouraging results.

Experimental work has shown that antitoxin to be effective must be given in excess before or very soon after the symptoms appear. Since a rapid determination of the type of organism producing the toxin is not possible, a polyvalent serum should be used. And since there is a possibility of *C. botulinum* producing its toxin in the body, the serum should be bacteriolytic or bactericidal as well as antitoxic. The serum should be injected intravenously. We have reason to hope that if antitoxin becomes generally available and is given to all those partaking of the suspected food as soon as the first patient shows symptoms, the death rate will be reduced materially.

22. McCaskey: Am. J. M. Sc. **158**:57 (July) 1919.

23. Ransom: Personal communication.

24. Randell: J. A. M. A. **75**:33 (July 3) 1920.

25. Jennings, Haass and Jennings: J. A. M. A. **74**:77 (Jan. 10) 1920.

26. Sisco: J. A. M. A. **74**:516 (Feb. 27) 1920.

## EFFECT OF FOODS ON THE TOXIN AND DEATH RATE

A review of available literature brought out certain facts which suggested to us that the foods in the stomach may have an influence on the appearance of the symptoms and the death rate.

The death rate in Europe is from 25 to 30 per cent. less than the death rate in the United States. This difference in the death rate may be due to a number of factors. The principal ones are the following:

1. The outbreaks in Europe are mainly due to toxin formed in foods such as meats, sausage and cheese, which are usually not preserved in liquids. The outbreaks in the United States have usually been due to toxins formed in foods preserved in liquids, such as fruits and vegetables. It is possible that the organism produces a stronger toxin in the latter foods; or that the liquid facilitates absorption.

2. Different habits in the heating and cooking of foods may reduce the death rate. Heat destroys the toxin.

3. The outbreaks in Europe may be due to a different type of *C. botulinum*, or to a prevalence of Type B, which usually produces a weaker toxin than Type A. The majority of the outbreaks in the United States have been produced by the toxin of Type A.

4. The Europeans use more oils and alcoholic drinks with meals. These may affect the rate of absorption or the strength of the toxin.

5. Botulism is not so well known as a specific disease in this country, and it is possible that only the fatal outbreaks have been recognized and reported.

The following facts have a bearing on the question concerning the effects on the toxin of food in the stomach. Occasionally, a person eating the toxic food escapes illness. The appearance of the symptoms in persons eating the same amount of the toxic food varies in time and severity. Variations in the appearance of the symptoms and the mortality may be due to the toxin not being evenly distributed through the food, to individual variation in resistance and to the effect of other foods taken into the stomach at the same time. Armstrong, Story and Scott<sup>25</sup> report that in the Canton, Ohio, outbreak two of those eating heavily of the toxic food escaped with slight symptoms and attribute this to the whisky taken with the meal. They were able to demonstrate that alcohol neutralizes the toxin when the two are mixed in a test tube. In the Boise, Idaho, outbreak one of those eating heavily of the toxic food escaped illness. Van Ermengem states that the toxin is precipitated by alcohol, tannin and neutral salts, and that 20 per cent. normal soda destroys it in a short time. Brieger and Kempner<sup>27</sup> state that the toxin in dried form is susceptible to alcohol,

27. Brieger and Kempner: Beitrag zur Lehre von der Fleischvergiftung. Deutsch. med. Wchnschr. 23:521, 1897.

ether and oxidizing agents. Forsman<sup>28</sup> reports that large doses placed in the large intestine of the rabbit produce no symptoms. The M. L. D. "per os" for rabbits is at least 300 times the subcutaneous M. L. D. These facts led us to investigate the effect of the stomach contents and various foods on the toxin of *C. botulinum*. We did not determine the effect of the contents of the intestines on the toxin or the potency of the toxin when introduced into the intestines.

*Experiment to determine the neutralizing action of the stomach contents of a normal rabbit on the toxin of C. botulinum.*—The contents of a full rabbit stomach was thoroughly dried in the incubator, then ground up in a mortar, mixed with an equal volume of diluted toxin and incubated two hours. The toxin used as a control was incubated at the same time. The toxin-stomach contents mixture was then centrifuged and the supernatant fluid injected subcutaneously into guinea-pigs. The results obtained (Table 6) indicate that the stomach contents of the rabbit do not neutralize or precipitate the toxin of *C. botulinum*.

TABLE 6.—RESULTS OF NEUTRALIZING ACTION OF STOMACH CONTENTS OF NORMAL RABBIT ON TOXIN OF *C. BOTULINUM*

Guinea-Pig	Amount Toxin	Results
Control 1	2 M. L. D. ....	Dead, 20 hours
Control 2	2 M. L. D., centrifuged toxin.....	Dead, 29 hours
Control 3	2 M. L. D., centrifuged toxin.....	Dead, 29 hours
4	2 M. L. D., toxin exposed to stomach contents.....	Dead, 29 hours
5	2 M. L. D., toxin exposed to stomach contents.....	Dead, 29 hours

The following experiment was designed to determine the comparative rates of absorption of the toxin in the full stomachs and starved stomachs of rabbits. Although the contents of a full rabbit stomach did not neutralize the toxin it was thought that it might affect the appearance of the symptoms and the death rate by mechanically slowing down the rate of absorption.

*Experiment to determine the effect of starving and the subsequent empty stomach on the rate of absorption of the toxin in the rabbit.*—Two rabbits were given water but no food for forty-eight hours. They were then given a small nibble of grass and force fed 4 c.c. of a toxic filtrate of *C. botulinum* Type B. The grass was fed to stimulate gastric secretion. Two normal rabbits received the same amount of toxin. The starved rabbits died before the controls. Starving the rabbits lowered their resistance to the toxin, or absorption of the toxin was more rapid in the empty stomachs. No experiments were made to determine which factor predominates. If the latter explanation is the

28. Forsman: Beiträge zur Kenntnis der Bakteriologie des Botulismus, Lunds Universitets Arsskrift, 1900; Abstr. Centralbl. f. Bakteriöl. 29:541, 1901.

true one then the amount of nontoxic food eaten by those at meals causing outbreaks of botulism may account for some of the variation in time of the appearance of the symptoms in the patients. The gastric juice apparently has no effect on the toxin. The results obtained (Table 7) suggest that in some outbreaks of botulism the amount of nontoxic food eaten may account for some of the variation in the time of the appearance of the symptoms in the victims and the degree of illness.

TABLE 7.—RESULTS OF STARVING AND SUBSEQUENT EMPTY STOMACH ON RATE OF ABSORPTION OF TOXIN IN RABBIT

Rabbit	Amount Toxin	Condition of Stomach	Results
1	4 c.c.	Full stomach.....	Dead in 144 hours
2	4 c.c.	Full stomach.....	Dead in 48 hours
3	4 c.c.	Starved 48 hours.....	Dead in 35 hours
4	4 c.c.	Starved 48 hours.....	Dead in 18 hours

Experiments were made to determine the effect of different human foods on the toxin of *C. botulinum*. It was thought that some foods might be more effective than others in slowing down the rate of absorption of the toxin. These experiments were designed to determine if the various foods afforded protection against the action of the toxin, if this protection was as great in the stomach as in subcutaneous injections and whether the protection was due to a neutralization of the toxin or to a slowing down of the rate of absorption.

#### FATS AND OILS

Kempner and Schepilewsky<sup>29</sup> state that butter and emulsified oil neutralize about twice the lethal dose of toxin for guinea-pigs when the fat and toxin are mixed and injected subcutaneously. McCaskey urges the use of "castor oil or some other laxative fat, for the double purpose of clearing out the ingested toxin, which is largely formed under saprophytic conditions, and of lowering or destroying the virulence by combination of fats." In consideration of these statements it seemed advisable to determine the extent of the protection afforded by the use of fats, the nature of this protection and if the protection afforded by different fats varied. Typical animal, vegetable and mineral fats and oils were used. The experiments described here are rather limited but the results obtained furnish the basis for certain conclusions which will be given under each experiment.

#### OLIVE OIL

*Experiment to Determine Whether Olive Oil Protects Against the Action of the Toxin of C. Botulinum.*—Different amounts of olive oil

29. Kempner and Schepilewsky: Ueber antitoxische Substanzen gegenüber dem Botulismusgift, Ztschr. f. Hyg. 27:213, 1898.

and a Type A toxin filtrate were used. The oil and toxin were placed in test tubes, emulsified by vigorous shaking and incubated one hour. The tubes were shaken several times during the incubation period. Injections were made subcutaneously into guinea-pigs. The results obtained (Table 8) show that guinea-pigs are protected from the action of the toxin of *C. botulinum* when the toxin and oil are emulsified in a test tube, incubated one hour and injected subcutaneously. Three c.c. of the oil protected against the action of 3 M. L. D. of the toxin but not against 4 M. L. D.

TABLE 8.—EFFECT OF OLIVE OIL AGAINST ACTION OF TOXIN OF *C. BOTULINUM* WHEN THE TWO ARE EMULSIFIED, INCUBATED AND INJECTED SUBCUTANEOUSLY?

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Olive Oil	Results
1	275	3 M. L. D.	.....	Dead, 20 hours
2	315	3 M. L. D.	3 c.c.	Lived
3	310	3 M. L. D.	6 c.c.	Lived
4	300	4 M. L. D.	3 c.c.	Dead, 70 hours
5	300	5 M. L. D.	5 c.c.	Dead, 96 hours

Experiments were made to determine whether the protection afforded by the olive oil was due to a neutralization of the toxin or to a slowing down of the rate of absorption. We assumed that if the protection afforded by the olive oil is due to a purely physical slowing down of the rate of absorption the following statements would prove to be true.

1. If the mixture, after incubation, is centrifuged the toxin in the water should not show any appreciable reduction in strength.
2. Emulsifying the toxin oil mixture several seconds should be just as effective as incubating several hours.
3. In intraperitoneal injections the protection afforded by the oil would be much less than that in subcutaneous injections and not such as could be accounted for by the difference in the M.L.D. for the two types of injections, and those receiving the oil-toxin mixture should die almost as soon as the controls. In intraperitoneal injections the rate of absorption is much greater.

*Experiment to determine whether the strength of the toxin of C. botulinum is reduced after exposure to olive oil.*—The same toxin and olive oil were used as in the preceding experiment. The toxin and olive oil were emulsified, incubated two hours and then centrifuged until the oil was free of water. The water was injected subcutaneously in guinea-pigs. The results obtained (Table 9) indicate that the strength of the toxin is affected slightly if at all by exposure to olive oil.

The experiment was repeated, with the exception that the injections were made intraperitoneally. The results obtained agree with those in the preceding experiment. The toxin control pig was dead in fifteen hours; the exposed toxin pig was dead in twenty-four hours and the mixture control pigs were dead in eighty-eight hours.

TABLE 9.—EFFECT OF OLIVE OIL ON THE STRENGTH OF THE TOXIN OF *C. BOTULINUM*

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Oil	Remarks	Result
1	365	3 M. L. D.	.....	Toxin control.....	Dead, 20 hours
2	300	3 M. L. D.	6 c.c.	Mixture control.....	Lived
3	315	3 M. L. D.	3 c.c.	Mixture control.....	Lived
4	325	3 M. L. D.	0 c.c.	Exposed toxin.....	Dead, 40 hours

*Experiment to determine whether emulsifying the toxin and olive oil and injecting immediately is just as effective in protecting against the action of the toxin as incubating two hours before injecting.*—The same toxin and olive oil was used as in the preceding experiment. The toxin and olive oil were placed in a test tube, shaken vigorously for 30 seconds and then injected subcutaneously into guinea-pigs. The control mixture was incubated two hours. The results obtained (Table 10) indicate that the incubation does not increase the protection afforded by the olive oil.

TABLE 10.—RESULTS OF EXPERIMENT TO DETERMINE WHETHER EMULSIFYING TOXIN AND OLIVE OIL AND INJECTING IMMEDIATELY IS JUST AS EFFECTIVE IN PROTECTING AGAINST ACTION OF TOXIN AS INCUBATING TWO HOURS BEFORE INJECTING

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Oil	Remarks	Result
1	365	5 M. L. D.	.....	Toxin control.....	Dead, 20 hours
2	275	5 M. L. D.	6 c.c.	Mixture incubated.....	Dead, 46 hours
3	265	5 M. L. D.	6 c.c.	Mixture not incubated.....	Dead, 50 hours
4	330	5 M. L. D.	6 c.c.	Mixture not incubated.....	Dead, 56 hours

The results of the above experiment with the olive oil convinced us that olive oil does not neutralize the toxin of *C. botulinum* and the experiments were discontinued. The protection afforded by the olive oil is probably due to a slowing down of the rate of absorption. It takes some time for the water containing the toxin to separate from the oil. This slowing down of the rate of absorption is sufficient to protect the guinea-pig from small amounts of toxin.

*Experiment to determine whether olive oil protects against the action of the toxin of C. botulinum in the stomach of the rabbit when force fed immediately after the toxin and at repeated intervals.*—Each rabbit was force fed 2.5 c.c. of a toxic filtrate, Type B. Ten c.c. of olive oil was force fed immediately after the toxin and at repeated intervals. The results obtained (Table 11) indicate that under the conditions of



this experiment olive oil affords a slight protection against the action of the toxin in the stomach of the rabbit. This protection is probably due to a slowing down of the rate of absorption of the toxin. The 2.5 c.c. of toxic filtrate used contained from 2 to 3 M. L. D. of toxin. It is possible that if 1 M. L. D. of toxin were used the protection afforded by the olive oil would be sufficient to save the life of the animal. Since the protection afforded by the olive oil is so slight and is of a physical nature, it is doubtful if it would have had any effect on the course of the disease if the treatment had been begun several hours after the toxin was administered.

TABLE 11.—EFFECT OF OLIVE OIL ON THE ACTION OF TOXIN OF *C. BOTULINUM* IN STOMACH OF RABBIT WHEN FORCE FED IMMEDIATELY AFTER TOXIN AND AT REPEATED INTERVALS

Rabbit	Weight, Gm.	Amount Toxin	Amount Oi	Hours Feeding Oil After Toxin	Results
1	2,300	2.5 c.c.	.....	.....	Dead, 15 hours
2	1,725	2.5 c.c.	.....	.....	Dead, 15 hours
3	1,260	2.5 c.c.	10 c.c.	0, 2, 18, 25	Dead, 39 hours
4	1,860	2.5 c.c.	10 c.c.	0, 2, 18, 25	Dead, 50 hours

#### LIQUID PETROLATUM

The experiments made with olive oil were repeated with liquid petrolatum as the neutralizing agent. The results obtained are similar to those obtained with olive oil. In experiments made by us the liquid petrolatum seemed to give less protection than the olive oil against the action of the toxin in subcutaneous injections and more protection than the olive oil in the stomach of the rabbit. It is assumed that the protection afforded by the liquid petrolatum is of the same nature as the protection afforded by the olive oil.

*Experiment to determine whether liquid petrolatum protects against the action of the toxin of C. botulinum when the two are emulsified, incubated and injected subcutaneously into guinea-pigs.*—The liquid petrolatum and a Type A toxic filtrate were mixed in a test tube, emulsified by vigorous shaking and incubated two hours. The mixture was shaken several times during the incubation period. The injections were made subcutaneously into guinea-pigs. The results obtained (Table 12) show that liquid petrolatum protects to a limited extent against the action of the toxin of *C. botulinum*. The guinea-pigs receiving the toxin-liquid petrolatum mixture lived several days longer than the toxin control.

*Experiment to determine whether liquid petrolatum protects against the action of the toxin of C. botulinum in the stomach of the rabbit when force fed immediately after the toxin and at repeated intervals.*—

This experiment was conducted in the same manner as the similar test with olive oil and the results obtained were approximately the same as with the olive oil. The animal receiving the liquid petrolatum lived eleven hours longer than the animal receiving the olive oil, a slight difference which we believe has no significance. The details of this experiment have no particular significance and are omitted for the sake of brevity. We hoped that a mineral oil which is unaffected by the action of the gastric juice would be more effective against the action of the toxin than a vegetable oil but such did not prove to be the case.

TABLE 12.—EFFECT OF LIQUID PETROLATUM AGAINST ACTION OF TOXIN OF *C. BOTULINUM* WHEN THE TWO ARE EMULSIFIED, INCUBATED AND INJECTED SUBCUTANEOUSLY

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Oil	Results
1	600	3 M. L. D.	.....	Dead, 29 hours
2	550	3 M. L. D.	3 c.c.	Dead, 170 hours
3	575	3 M. L. D.	6 c.c.	Dead, 168 hours

#### BUTTER

Our experiments with butter indicate that it affords less protection against the action of the toxin of *C. botulinum* than olive oil or liquid petrolatum. This is probably due to some physical difference between the butter and the oils. The water containing the toxin seemed to separate from the butter more rapidly than from the oils. If the protection against the toxin afforded by fats depends upon a slowing down of the rate of absorption then the amount of protection afforded by any fat depends on the rate of separation of the water from the fat.

TABLE 13.—EFFECT OF BUTTER AGAINST ACTION OF TOXIN OF *C. BOTULINUM* WHEN THE TWO ARE EMULSIFIED, INCUBATED AND INJECTED SUBCUTANEOUSLY INTO GUINEA-PIGS

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Butter	Results
1	450	3 M. L. D.	.....	Dead, 21 hours
2	350	3 M. L. D.	3 c.c.	Dead, 35 hours
3	450	3 M. L. D.	6 c.c.	Dead, 50 hours

*Experiment to determine whether butter protects against the action of the toxin of C. botulinum when the two are emulsified, incubated and injected subcutaneously into guinea-pigs.*—The butter was melted, emulsified with a type B filtrate and incubated two hours. The emulsion was shaken several times during the incubation period. Injections were made subcutaneously into guinea-pigs. The results obtained (Table 13) indicate that butter has a slight retarding action on the toxin of *C. botulinum*. We believe this action is due to a slowing down

of the rate of absorption and that butter does not protect against the toxin as well as olive oil because the emulsion breaks down more rapidly.

MILK, EGG WHITE, EGG YOLK, SUGAR, BRAIN, GELATIN

Kempner and Schepilewsky<sup>30</sup> state that the brain tissue of a guinea-pig will neutralize from 3 to 4 M. L. D. of toxin if the brain tissue and toxin are mixed in a test tube and that some protection is afforded by the brain tissue if injected separately from the toxin. Our experiments indicate that the brain tissue of the sheep has no special affinity for the toxin of *C. botulinum* and in "in vitro" injections affords little or no protection.

*Experiment to determine whether milk, egg white, egg yolk, sugar, brain tissue and gelatin afford as great protection against the action of the toxin of C. botulinum as olive oil.*—The brain tissue was ground up and squeezed through cheese cloth. A type B toxin filtrate was used. All mixtures were shaken thoroughly, incubated 1 hour and injected subcutaneously into guinea-pigs. The results obtained (Table 14) indicate that in subcutaneous injections the protection afforded by these food substances is not equal to that of olive oil.

TABLE 14.—RESULT OF AN EXPERIMENT TO DETERMINE WHETHER MILK, EGG WHITE, EGG YOLK, SUGAR, BRAIN TISSUE AND GELATIN AFFORD AS GREAT PROTECTION AS OLIVE OIL AGAINST ACTION OF TOXIN OF *C. BOTULINUM*

Guinea-Pig	Amount Toxin	Amount Neutralizing Agent	Results
1	3 M. L. D.	.....	Dead in 20 hours
2	3 M. L. D.	3 c.c. olive oil.....	Lived
3	4 M. L. D.	3 c.c. olive oil.....	Dead in 70 hours
4	2 M. L. D.	4 c.c. milk.....	Dead in 20 hours
5	2 M. L. D.	1 c.c. 25% solution glucose.....	Dead in 42 hours
6	2 M. L. D.	3 c.c. egg white.....	Dead in 40 hours
7	2 M. L. D.	3 c.c. egg yolk.....	Dead in 40 hours
8	2 M. L. D.	3 gm. sheep brain.....	Dead in 36 hours
9	3 M. L. D.	3 c.c. 20% gelatin in water.....	Dead in 35 hours

#### VINEGAR

A number of outbreaks of botulism have followed the eating of salads containing the poisonous food. We considered it advisable to determine whether any of the ingredients of ordinary salad dressing would affect the action of the toxin. The three common ingredients of salad dressings are olive oil, egg and vinegar. We have already shown that olive oil affords some protection against the action of the toxin of *C. botulinum* and that egg affords little or no protection. We record here our experiments with vinegar.

*Experiment to determine whether vinegar affords protection against the action of the toxin of C. botulinum when the two are mixed in a test tube, incubated two hours and injected subcutaneously into guinea-*

30. Kempner and Schepilewsky: Ueber antitoxische Substanzen gegenüber dem Botulismusgift. Ztschr. f. Hyg. 27:213, 1898.

pigs.—A Type B toxin filtrate and apple vinegar were used. The toxin and vinegar were mixed in a test tube and incubated two hours and injected subcutaneously in guinea-pigs. The results obtained (Table 15) show that 3 c.c. of the apple vinegar used protected against the action of a 4 M. L. D. of toxin.

It was found that the vinegar caused considerable necrosis, and the possibility of this accounting for the protection against the toxin was considered. It was thought that the necrosis might slow down the rate of absorption and the necrotic cells absorb some of the toxin.

TABLE 15.—EFFECT OF VINEGAR AGAINST ACTION OF TOXIN OF *C. BOTULINUM* WHEN THE TWO ARE MIXED, INCUBATED TWO HOURS AND INJECTED SUBCUTANEOUSLY

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Vinegar	Result
1	415	4 M. L. D.	.....	Dead in 15 hours
2	400	.....	3 c.c.	Lived
3	405	4 M. L. D.	3 c.c.	Dead in 84 hours
4	400	4 M. L. D.	3 c.c.	Lived

TABLE 16.—RESULTS OF AN EXPERIMENT TO DETERMINE WHETHER THE PROTECTION AFFORDED BY VINEGAR AGAINST ACTION OF TOXIN OF *C. BOTULINUM* IS DUE TO NECROSIS OF TISSUES OR TO ACETIC ACID PRESENT IN VINEGAR

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Vinegar	Remarks	Results
1	415	4 M. L. D.	.....	.....	Dead, 15 hours
2	430	4 M. L. D.	3 c.c.	Neutralized with sodium hydroxid just before injecting.....	Lived
3	415	4 M. L. D.	3 c.c.	Neutralized before adding to toxin	Lived
4	275	8 M. L. D.	1 c.c.	Neutralized before adding to toxin	Dead, 27 hours
5	280	20 M. L. D.	1 c.c.	Neutralized before adding to toxin	Dead, 15 hours
6	275	200 M. L. D.	1 c.c.	Neutralized before adding to toxin	Dead, 15 hours

*Experiment to determine whether the protection afforded by vinegar against the action of the toxin of C. botulinum is due to a neutralization of the toxin or to a necrosis of the tissues or to the acetic acid present in the vinegar.*—Vinegar neutralized with sodium hydroxid causes little or no necrosis. The toxin filtrate and vinegar were mixed, incubated two hours, neutralized with normal sodium hydroxid and injected subcutaneously into guinea-pigs. To determine whether neutralized vinegar protects against the action of the toxin, vinegar was neutralized with normal sodium hydroxid, mixed with the toxin, incubated and injected subcutaneously into guinea-pigs. The results obtained (Table 16) indicate that the protection afforded by the vinegar is not due to the necrosis of the tissues. They also indicate that the action on the toxin is not due to the acid in the vinegar since the neutralized vinegar also protects against the action of the toxin.

*Experiment to determine whether acetic acid, sodium acetate and sodium hydroxid will protect against the action of the toxin of C.*

*botulinum* when mixed with the toxin incubated and injected subcutaneously into guinea-pigs.—A Type B toxin filtrate was used. The amount of normal sodium hydroxid used was the same as that used to neutralize the 3 c.c. of vinegar. The amount of acetic acid used was the amount required to neutralize the sodium hydroxid. Controls with acetic acid and normal sodium hydroxid were not made. The mixtures were incubated two hours before being injected subcutaneously into guinea-pigs. The results obtained (Table 17) show that acetic acid and sodium acetate do not neutralize the toxin of *C. botulinum*. The guinea-pig receiving the sodium hydroxid-toxin mixture neutralized just before injecting lived nine days. The animal receiving sodium hydroxid toxin mixture unneutralized died in fourteen days. The death of this animal may have been due to the alkali rather than to the toxin, as the whole lower part of the body was greatly swollen. The animal receiving the sodium hydroxid neutralized with acetic acid before the toxin was added died. The protection afforded by the sodium hydroxid apparently is not due to a slowing down of the rate of absorption of the toxin as there was no evidence of necrosis in the animal living nine days. The results obtained with the sodium hydroxid suggest that it neutralizes the action of the toxin to some extent.

TABLE 17.—EFFECT OF ACETIC ACID, SODIUM ACETATE AND SODIUM HYDROXID AGAINST ACTION OF TOXIN OF *C. BOTULINUM* WHEN MIXED WITH TOXIN, INCUBATED AND INJECTED SUBCUTANEOUSLY

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Neutral Agent and Remarks	Results
1	275	4 M. L. D.	1 c.c. salt solution.....	Dead, 15 hours
2	275	4 M. L. D.	2.4 c.c. normal acetic acid. Neutralized with normal sodium hydroxid just before injecting.....	Dead, 15 hours
3	285	4 M. L. D.	2.4 c.c. normal acetic acid. Neutralized with normal sodium hydroxid before adding to toxin.....	Dead, 36 hours
4	290	4 M. L. D.	2.4 c.c. normal sodium hydroxid.....	Dead, 36 hours
5	300	4 M. L. D.	2.4 c.c. normal sodium hydroxid neutralized with normal acetic acid just before injecting.....	Dead, 14 days
6	400	4 M. L. D.	0.04 gm. sodium acetate.....	Dead, 9 days
7	310	4 M. L. D.	0.04 gm. sodium acetate.....	Dead, 26 hours
8	325	4 M. L. D.	0.04 gm. sodium acetate.....	Lived

These experiments have not determined the active agent in the protection afforded by vinegar or vinegar neutralized with normal sodium hydroxid. We apparently have eliminated acetic acid as a factor in the first case and sodium acetate as a factor in the second case. Since sodium hydroxid reduces the virulence of the toxin, we have not eliminated the possibility of the protection afforded by the vinegar being due to necrosis of the tissues and the protection afforded by the neutralized vinegar being due to some action of the sodium hydroxid. As we have shown that sodium hydroxid neutralized with acetic acid does not reduce the virulence of the toxin we believe that the protection afforded by the vinegar is not due entirely to necrosis but to some factor

not determined by us. A qualitative test for alcohol was positive. Our experiments were discontinued at this point. Armstrong, Story and Scott state that alcohol neutralizes the toxin of *C. botulinum*. The small amount of alcohol in the vinegar may account for its neutralizing action on the toxin. Further experiments with vinegar should be made. In this connection it is interesting to note that Dickson,<sup>8</sup> quoting Schreiber and Hirschfeldt, reports two outbreaks of food poisoning following the eating of herring preserved in vinegar. Also, some of the outbreaks of botulism in this country followed the eating of salads containing vinegar and olive oil.

TABLE 18.—EFFECT OF VINEGAR AGAINST ACTION OF TOXIN OF *C. BOTULINUM* IN STOMACH OF RABBIT WHEN FORCE FED IMMEDIATELY AFTER TOXIN AND AT REPEATED INTERVALS

Rabbit	Weight, Gm.	Amount Toxin	Amount Vinegar	Hours After Feeding Toxin	Results
1	2,300	2.5 c.c.	.....	.....	Dead, 15 hours
2	1,725	2.5 c.c.	.....	.....	Dead, 15 hours
3	1,360	2.5 c.c.	10 c.c. water	0, 2, 18, 25	Dead, 39 hours
4	1,465	2.5 c.c.	5 c.c. vinegar	0, 2, 18	Lived

*Experiment to determine whether vinegar protects against the action of the toxin of C. botulinum in the stomach of the rabbit when force fed immediately after the toxin and at repeated intervals.*—A Type B toxin filtrate was used. The amount given was approximately 2 M. L. D. The rabbits were fed 5 c.c. vinegar at each treatment, receiving a total amount of 15 c.c. The results obtained (Table 18) indicate that vinegar affords some protection against the action of the toxin in the stomach of the rabbit.

#### GRAM'S IODIN SOLUTION

*Experiment to determine whether Gram's solution protects against the action of the toxin of C. botulinum when the two are mixed, incubated and injected subcutaneously into guinea-pigs.*—A Type B toxin filtrate was used. The Gram solution was mixed with the toxin, incubated two hours and injected subcutaneously into guinea-pigs. The results obtained (Table 19) indicate that this solution protects against the action of the toxin of *C. botulinum*. A guinea-pig was saved from the effects of 8 M. L. D. of toxin by 0.1 c.c. of Gram's solution.

*Experiment to determine whether Gram's solution will protect against the action of the toxin of C. botulinum when injected separately from the toxin.*—A Type B toxin was used. Repeated injections of Gram's solution were made on the opposite side of the body of the guinea-pigs from the toxin. The injections were begun before or at the same time the toxin was injected. To prevent the iodine causing

necrosis of the tissues, 70 mg. of corn starch were added to each cubic centimeter of the Gram solution. The iodine injections were repeated at three hour intervals. The results obtained (Table 20) indicate that Gram's solution when injected separately from the toxin offers no protection.

TABLE 19.—EFFECT OF GRAM'S SOLUTION AGAINST ACTION OF TOXIN OF *C. BOTULINUM* WHEN THE TWO ARE MIXED, INCUBATED AND INJECTED SUBCUTANEOUSLY INTO GUINEA-PIGS

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Gram's Solution	Results
1	420	4 M. L. D.	.....	Dead, 28 hours
2	345	8 M. L. D.	.....	Dead, 15 hours
3	275	4 M. L. D.	.....	Dead, 15 hours
4	450	4 M. L. D.	1.5 c.c.	Lived
5	260	4 M. L. D.	0.5 c.c.	Lived
6	275	4 M. L. D.	0.6 c.c.	Lived
7	270	4 M. L. D.	0.4 c.c.	Lived
8	260	4 M. L. D.	0.1 c.c.	Lived
9	345	8 M. L. D.	0.1 c.c.	Lived
10	335	20 M. L. D.	0.1 c.c.	Dead in 40 hours
11	320	200 M. L. D.	0.1 c.c.	Dead in 15 hours

TABLE 20.—EFFECT OF GRAM'S SOLUTION AGAINST ACTION OF TOXIN OF *C. BOTULINUM* WHEN INJECTED SEPARATELY FROM THE TOXIN

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Gram's Solution	Hours Injected After Toxin	Results
1	315	2 M. L. D.	.....	.....	Dead, 35 hours
2	315	2 M. L. D.	4 c.c.	0, 3, 5, 9	Dead, 29 hours
3	280	2 M. L. D.	4 c.c.	3, 0, 3, 5, 9	Dead, 31 hours

TABLE 21.—RESULT OF EXPERIMENT TO DETERMINE WHETHER THE PROTECTION AFFORDED BY GRAM'S SOLUTION AGAINST ACTION OF TOXIN OF *C. BOTULINUM* IS DUE TO THE NECROSIS OF THE TISSUE, TO THE POTASSIUM IODID OR TO THE IODINE

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Neutralizing Agent and Remarks	Results
1	335	4 M. L. D.	.....	Dead, 15 hours
2	450	4 M. L. D.	1.5 c.c. Gram's solution.....	Lived
3	465	4 M. L. D.	1.5 c.c. Gram's solution, starch added just before injecting.....	Lived
4	460	4 M. L. D.	1.5 c.c. Gram's solution, starch added before the toxin.....	Lived
5	450	4 M. L. D.	3 c.c. saturated solution of iodine.....	Lived
6	420	4 M. L. D.	1.5 c.c. 2% potassium iodid.....	Dead, 40 hours
8	435	4 M. L. D.	105 mg. corn starch in salt solution....	Dead, 28 hours
7	210	4 M. L. D.	4.5 c.c. 2% potassium iodid.....	Dead, 27 hours

*Experiment to determine whether the protection afforded by Gram's solution against the action of the toxin of C. botulinum is due to the necrosis of the tissues, to the potassium iodid or to the iodine.*—A Type B toxin filtrate, a 2 per cent. solution of potassium iodid and a saturated aqueous solution of iodine were used. Seventy mg. of corn starch were added to each cubic centimeter of the iodine solution to prevent necrosis of the tissues. The toxin and solutions were mixed, incubated two hours

and injected subcutaneously into guinea-pigs. The animals receiving the Gram solution, the Gram iodine starch mixture and the saturated solution of iodine lived. The animal receiving the potassium iodide died about the same time as the controls. The results obtained (Table 21) show that the protection afforded by Gram's solution is not due entirely to necrosis of the tissues or to the potassium iodide present, but to the iodine.

*Experiment to determine whether Gram's solution neutralized with corn starch is just as effective as unneutralized Gram's solution in protecting against the action of the toxin of C. botulinum.*—A Type B toxin filtrate was used. To neutralize the action of the Gram's solution on the tissues, 70 mg. of corn starch was added to each cubic centimeter. The toxin was mixed with the solutions, incubated two hours and injected subcutaneously into guinea-pigs. The results obtained (Table 22) indicate that the addition of starch to the Gram solution slightly reduces its protective action against the toxin. The increased protection afforded by the unneutralized Gram's solution may be due to its action on the tissues.

TABLE 22.—RESULTS OF EXPERIMENT TO DETERMINE WHETHER GRAM'S SOLUTION NEUTRALIZED WITH CORN STARCH IS JUST AS EFFECTIVE AS UNNEUTRALIZED GRAM'S SOLUTION IN PROTECTING AGAINST ACTION OF TOXIN OF C. BOTULINUM

Guinea-Pig	Weight	Amount Toxin	Amount Neutralizing Agent	Result
1	420	4 M. L. D.	.....	Dead, 28 hours
2	275	4 M. L. D.	.....	Dead, 15 hours
3	260	4 M. L. D.	0.1 c.c. Gram's solution.....	Lived
4	343	8 M. L. D.	0.1 c.c. Gram's solution.....	Lived
5	335	20 M. L. D.	0.1 c.c. Gram's solution.....	Dead, 40 hours
6	320	200 M. L. D.	0.1 c.c. Gram's solution.....	Dead, 15 hours
7	465	4 M. L. D.	0.4 c.c. neutralizing Gram's solution	Lived
8	380	8 M. L. D.	0.4 c.c. neutralizing Gram's solution	Dead, 110 hours
9	300	20 M. L. D.	0.4 c.c. neutralizing Gram's solution	Dead, 18 hours
10	385	200 M. L. D.	0.4 c.c. neutralizing Gram's solution	Dead, 15 hours

TABLE 23.—EFFECT OF GRAM'S SOLUTION AGAINST ACTION OF TOXIN OF C. BOTULINUM IN STOMACH OF RABBIT WHEN FORCE FED IMMEDIATELY AFTER TOXIC CULTURE AND AT REPEATED INTERVALS

Rabbit	Amount Toxic Culture	Amount Gram's Solution	Hours After Toxin	Results
1	6 c.c.	.....	.....	Dead, 17 hours
2	6 c.c.	.....	.....	Dead, 30 hours
3	6 c.c.	4 c.c.	0	Dead, 3 hours
4	6 c.c.	4 c.c.	0, 2, 4	Lived

*Experiment to determine whether Gram's solution will protect against the action of the toxin of C. botulinum in the stomach of the rabbit when force fed immediately after a toxic culture and at repeated intervals.*—Each rabbit received 6 c.c. of a toxic meat culture of C. botulinum Type B. Four c.c. of Gram's solution was used at each



treatment. This is an extreme dose and will kill some of the rabbits before the toxin has time to act. We did not test the effect of a Gram iodine-starch solution. The Gram solution is a strong disinfectant and should destroy the organisms reached as well as the toxin. In our short series of experiments one of the rabbits receiving the Gram solution after the toxin lived, indicating that the iodine has some neutralizing action on the toxin in the stomach of a rabbit (Table 23).

#### LIQUID SOAP

We have already shown that sodium hydroxide has a neutralizing action on the toxin of *C. botulinum*. Since soap contains an alkali and may be used in the preparation of enemas, we undertook to determine whether liquid soap would protect against the action of the toxin of *C. botulinum*. The soap used did not change the color of either litmus paper or phenolphthalein paper.

TABLE 24.—EFFECT OF LIQUID SOAP AGAINST ACTION OF TOXIN OF *C. BOTULINUM* WHEN THE TWO ARE MIXED, INCUBATED AND INJECTED SUBCUTANEOUSLY

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Soap	Remarks	Results
1	275	4 M. L. D.	.....	.....	Dead, 15 hours
2	305	4 M. L. D.	1 c.c.	3 c.c. salt solution added just before injecting...	Lived
3	315	8 M. L. D.	1 c.c.	3 c.c. salt solution added just before injecting...	Lived
4	330	20 M. L. D.	1 c.c.	3 c.c. salt solution added just before injecting...	Lived
5	325	200 M. L. D.	1 c.c.	3 c.c. salt solution added just before injecting...	Lived

*Experiment to determine whether liquid soap will protect against the action of the toxin of C. botulinum when the two are mixed, incubated and injected subcutaneously into guinea-pigs.*—A Type B. toxin filtrate was used. Subcutaneous injection of the soap caused considerable necrosis and occasionally death. The addition of salt solution was found to prevent this, and in these experiments 3 c.c. of physiologic sodium chloride solution were added to each cubic centimeter of soap used. The salt solution was added to the toxin-soap mixture after the incubation period. The toxin-soap mixtures were incubated two hours, the salt solution added, and then injected subcutaneously into guinea-pigs. The results obtained (Table 24) show that 1 c.c. of the liquid soap used protected a guinea-pig from at least 20 M. L. D. of toxin. No attempt was made to determine the active agent in the neutralization of the toxin, but we believe that the alkali in the soap neutralized the toxin. We found that glycerin has no effect on the toxin.

Experiments to determine the action of soap on the toxin in the stomach of rabbits was begun but were not carried far enough to war-

rant description. In our preliminary experiments in force feeding soap, the animals died in a few hours from the effects of the soap. Experiments should be made to determine whether the soap can be diluted sufficiently not to injure the rabbit fatally and retain its action on the toxin. The action of the soap on the toxin in the intestines should also be demonstrated. Experiments with soap might lead to some treatment of value.

#### MISCELLANEOUS FEEDING EXPERIMENTS

Drawing any conclusions from the results of a short series of feeding experiments is very unsatisfactory. This is particularly true when feeding small amounts of toxin and basing the conclusions on the time of appearance of the symptoms or the time of death. However, these are conditions that are difficult to avoid. We are dealing with a powerful toxin and we cannot hope for more than a slight protection from any nonspecific treatment. In subcutaneous injections the lethal dose can be accurately determined and remains fairly constant for animals of the same weight. This is not true in feeding experiments. As a result of our experiment to determine the effect of a full rabbit stomach on the action of the toxin, we believe that the amount of food in the rabbit stomach at the time the animal is fed will affect the time of death. Also, if the feeding tube penetrates the mass of food in the stomach and the toxin is deposited in the center of the food mass, absorption will be delayed. Some rabbits readily take food after the toxin is fed, others eat sparingly or not at all. In order to discount these factors, we used two toxin controls and sufficient toxin to insure death in less than forty-eight hours. Presumably any animal living longer than forty-eight hours was protected to some extent by the substance being tested. The amount of toxin used was such that in most cases the toxin controls were dead in fifteen hours. While the animals living longer than forty-eight hours apparently were protected to some extent, it is possible that some of the animals dying between twenty-four and forty-eight hours were also slightly protected.

We believe that with most of the substances used by us the main factor in the protection afforded is a slowing down of the rate of absorption. We have shown in subcutaneous injection that by mixing the toxin with olive oil, the rate of absorption is slowed down to such an extent that guinea-pigs will resist three lethal doses. The rate of absorption of the toxin from the stomach affects the time of the appearance of symptoms and of death. And, in case a small amount of toxin is ingested, any slowing down of the rate of absorption may prevent death.

When it became evident that our investigations must be terminated, we carried out a number of feeding experiments. We had already shown that some of the substances used had no effect on the toxin when mixed with it and injected subcutaneously. It was thought, however, that they might delay the appearance of the symptoms when force fed into the stomach immediately after the toxin. The results obtained would, at least, have some bearing on our belief that the amount and kind of food taken with the toxin materially affects the time of appearance and severity of the symptoms. Also, these non-neutralizing substances might have more effect on the toxin after coming in contact with and being altered by the gastric juice. Other of these substances had been shown to protect against the action of the toxin in subcutaneous injections. It was thought that these might not have any effect on the toxin in the stomach as a result of being altered by contact with the gastric juice before coming in contact with the toxin.

*Experiment to determine the effect of milk, turpentine, alcohol, a proprietary nerve tonic and water on the toxin in the stomach of the rabbit when force fed immediately after the toxin and at repeated intervals.*—About 2 M. L. D. of Type B toxin was used; this required 2.5 c.c. of the filtrate. We have shown that milk does not neutralize or protect against the action of the toxin in subcutaneous injections. Armstrong, Story and Scott have shown that alcohol will protect against the action of the toxin when the two are mixed and injected subcutaneously. We used a 30 per cent. solution of alcohol. While testing the protective properties of miscellaneous substances it was suggested that the effects of a proprietary nerve tonic be determined. According to the label this tonic contained 14 per cent. alcohol, and each fluid ounce contained 8 grains sodium glycerophosphate, 4 grains calcium glycerophosphate, 4 grains potassium glycerophosphate,  $\frac{1}{60}$  grain strychnin glycerophosphate,  $\frac{1}{16}$  grain lecithin and  $\frac{1}{30}$  grain avenin. The tonic was used without diluting. These substances were force fed immediately after the toxin and at repeated intervals. The results obtained (Table 25) indicate that either numerous substances have a slight effect on the action of the toxin in the stomach of the rabbit, or that none of the substances used had any effect, and the results obtained simply represent individual variation in resistance to the toxin. Rabbits do show considerable variation in resistance to force fed toxin. We believe, however, that our results indicate something more than individual variation or error in technic. In experiments of this kind in which we are endeavoring to determine or measure slight effects and in which all the factors cannot be controlled, long series of experiments should be made. We have not had an opportunity to do this.

TABLE 25.—RESULTS OF EXPERIMENTS TO DETERMINE EFFECT OF MILK, TURPENTINE, ALCOHOL, A PROPRIETARY NERVE TONIC AND WATER ON THE TOXIN OF *C. BOTULINUM* IN THE STOMACH OF RABBIT WHEN FORCE FED IMMEDIATELY AFTER TOXIN AND AT REPEATED INTERVALS

Rabbit	Weight, Gm.	Amount Toxin	Amount Neutralizing Agent	Injections Hours After Toxin	Results
1	2,300	2.5 c.c.	.....	.....	Dead, 15 hours
2	1,725	2.5 c.c.	.....	.....	Dead, 15 hours
3	1,675	2.5 c.c.	10 c.c. milk.....	0, 2, 18, 25	Dead, 87 hours
4	1,575	2.5 c.c.	5 c.c. tonic.....	0, 2, 18, 25	Lived
5	1,800	2.5 c.c.	4 c.c. turpentine..	0, 5	Dead, 80 hours
6	2,000	2.5 c.c.	4 c.c. 30% alcohol	0, 5	Dead, 73 hours
7	1,260	2.5 c.c.	15 c.c. water.....	0, 2, 18, 25	Dead, 39 hours

## EPINEPHRIN

Marie<sup>31</sup> states that epinephrin neutralizes the soluble toxins of tetanus and diphtheria. He shows that epinephrin will protect against lethal doses of the toxins both in "in vitro" and in "in vivo" experiments. Our experiments indicate that epinephrin chlorid affords some protection against lethal doses of the toxin of *C. botulinum* when the two are mixed and injected subcutaneously.

*Experiment to determine whether epinephrin chlorid will protect against the action of the toxin of C. botulinum when the two are mixed, incubated and injected subcutaneously into guinea-pigs.*—A Type B toxin filtrate and the ordinary commercial epinephrin chlorid solution, 1:1,000, were used. The toxin and epinephrin solution were mixed, incubated two hours and injected subcutaneously in guinea-pigs. The results obtained (Table 26) indicate that epinephrin chlorid solution has some neutralizing action on the toxin of *C. botulinum*. Experiments should be made to determine whether the action of epinephrin on the body influences the course of the disease.

TABLE 26.—EFFECT OF EPINEPHRIN CHLORID AGAINST ACTION OF TOXIN OF *C. BOTULINUM* WHEN THE TWO ARE MIXED, INCUBATED AND INJECTED SUBCUTANEOUSLY

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Epinephrin	Results
1	175	3 M. L. D.	.....	Dead, 18 hours
2	200	.....	0.1 c.c.	Lived
3	200	3 M. L. D.	0.1 c.c.	Dead, 42 hours
4	210	3 M. L. D.	0.2 c.c.	Dead, 60 hours

## POTASSIUM PERMANGANATE

*Experiment to determine whether potassium permanganate will protect against the action of the toxin of C. botulinum when the two are mixed, incubated and injected subcutaneously in guinea-pigs.*—A

33. Marie: Du mode d'action de l'adrenaline vis a vis des toxines solubles. *Compt. rend. Soc. de biol.* **82**: 1919; Du mode d'action de l'adrenaline sur les toxines bacteriennes, *Ann. de l'Inst. Pasteur* **33**:645, 1919.

Type A toxin filtrate and a 1 per cent. water solution of potassium permanganate were used. The toxin and potassium permanganate solution were mixed, incubated two hours and injected subcutaneously into guinea-pigs. The results obtained (Table 27) indicate that 1 c.c. of a 1 per cent. solution of potassium permanganate will protect a guinea-pig from at least 6 M. L. D. of toxin. The potassium permanganate causes considerable necrosis of the tissues. No attempt was made to determine if the necrosis is a factor in the protection afforded by the potassium permanganate.

TABLE 27.—EFFECT OF POTASSIUM PERMANGANATE AGAINST ACTION OF TOXIN OF *C. BOTULINUM* WHEN THE TWO ARE MIXED, INCUBATED AND INJECTED SUBCUTANEOUSLY

Guinea-Pig	Amount Toxin	Amount Potassium Permanganate	Result
1	2 M. L. D.	.....	Dead, 36 hours
2	2 M. L. D.	1 c.c.	Dead, 15 days
3	3 M. L. D.	1 c.c.	Lived
4	4 M. L. D.	1 c.c.	Lived
5	6 M. L. D.	1 c.c.	Lived

#### CONCLUSIONS

1. Spoiled foods containing gas may appear to be boiling for several minutes before the true boiling point is reached. We recommend that all suspected food be subjected to vigorous boiling for at least thirty minutes before being tasted.

2. Spoiled canned foods giving the appearance of boiling for seven minutes and subjected to actual boiling for four minutes are not safe to eat. Spoiled canned foods exposed to a temperature of 80 C. for one hour may appear to be boiling part of the time and not be safe to eat.

3. We may expect to have outbreaks of botulism following the eating of insufficiently cooked spoiled foods.

4. The heat resistance of the disease producing power of different kinds of spoiled canned foods containing *C. botulinum* and its toxin has not been determined and probably will be found to vary.

5. There have been no recorded outbreaks of botulism in this country without a history of preserved foods having been eaten.

6. There is no evidence that infection in man ever follows the ingestion of toxin free organisms of *C. botulinum*.

7. There is no evidence that infection in man ever follows the ingestion of the toxin and organisms of *C. botulinum*.

8. Botulism does not result from the ingestion of small numbers of toxin free spores.

9. The disease producing power of an old can of spoiled beans containing *C. botulinum* and its toxin can be destroyed by an exposure to temperatures that rarely if ever destroy the spores of *C. botulinum*.

10. Rabbits can be saved from the effects of feeding 2 M. L. D. of a toxic culture of *C. botulinum* by the intravenous injection of the homologous antitoxin as soon as the symptoms appear. Such rabbits cannot be saved if the antitoxin treatment is delayed until the symptoms are well advanced.

11. In outbreaks of botulism, as soon as the first case develops, a polyvalent immune serum should be injected intravenously in all those who have partaken of the suspected meal. This treatment should materially decrease the death rate.

12. The contents of a full normal rabbit stomach does not neutralize the toxin of *C. botulinum* but it apparently reduces the action of the toxin to some extent by slowing down or preventing its absorption.

13. Fats and oils do not neutralize the toxin of *C. botulinum*.

14. Fats and oils will protect against the action of the toxin of *C. botulinum* when the toxin and fat or oil are emulsified and injected subcutaneously into guinea-pigs. This protection is very limited and varies with the degree of the emulsion and the type of fat. The protection is due to a slowing down of the rate of absorption of the toxin.

15. Olive oil will delay the action of the toxin in the stomach of a rabbit when force fed immediately after the toxin and at repeated intervals. It apparently affords no greater protection than milk.

16. Certain food substances, such as glucose, brain tissue, milk, eggs and gelatin do not neutralize the toxin of *C. botulinum* and do not protect as effectively as olive oil against the action of the toxin in subcutaneous injections.

17. Apple vinegar, giving a positive test for alcohol, protects against the action of the toxin of *C. botulinum* when the two are mixed, incubated two hours and injected subcutaneously into guinea-pigs.

18. The protection afforded by the vinegar is not due to necrosis of the tissues, since vinegar neutralized with sodium hydroxid does not cause necrosis, and still protects against the action of the toxin. The protection afforded by the vinegar may be due to the alcohol present. Acetic acid and sodium acetate do not neutralize the toxin of *C. botulinum*.

19. Vinegar when force fed immediately after a toxin filtrate and at repeated intervals afforded some protection against the action of the toxin in the stomach of the rabbit.

20. Sodium hydroxid, potassium permanganate and liquid soap have a neutralizing action on the toxin of *C. botulinum*.

21. Epinephrin chlorid has a slight neutralizing action on the toxin of *C. botulinum*.

22. Iodin and iodine to which sufficient starch has been added to prevent necrosis of the tissues has a strong neutralizing action on the toxin of *C. botulinum*. Potassium iodide does not neutralize the toxin of *C. botulinum*. In "in vivo" experiments, iodine injected on the opposite side of the body from the toxin afforded no protection. Gram's solution affords some protection against the action of the toxin in the stomach of the rabbit when force fed immediately after the toxin.

#### SUMMARY

The treatment of botulism is in the experimental stage, and based mainly on insufficient or inexact knowledge. In experimental work with laboratory animals and in the treatment of human cases of botulism there has not been gained sufficient knowledge to develop a scientific treatment. This can be explained partly on the grounds that it is only within the past few years that the attention of the investigators has been drawn to the subject of botulism and partly to the fact that we are dealing with a powerful and rapidly acting toxin. However, we have reasons to believe that when further experimental work has been done, and physicians become better acquainted with the disease, a treatment will be developed that will materially lessen the death rate.

*Specific Treatment.*—The treatment of botulism may be classed as specific and general. By specific treatment we mean the use of an immune serum which neutralizes the specific toxin of *C. botulinum*. Since there are at least two distinct toxins, and there is no rapid means of determining the type, it is necessary to use a polyvalent antitoxin or a Type A and a Type B antitoxin. And since there is a possibility that *C. botulinum* occasionally produces its toxin in the body, the immune serum should be bacteriolytic or bactericidal as well as antitoxic. The serum should be injected intravenously.

The immune serum to be beneficial must be used as soon as possible after the diagnosis is made. In all cases of doubtful diagnosis, all of those having partaken of the suspected meal should receive immediate antitoxin treatment. The antitoxin can only neutralize the toxin and prevent further injury. It is of no value to the already damaged nervous system. The evidence we have indicates that treatment begun after the symptoms are well advanced will not, in most cases, alter the course of the disease. But we have sufficient experimental evidence to believe that some of those receiving lethal amounts of toxin can be saved by the use of antitoxin if the treatment is begun at about or before the time the symptoms appear.

*General Treatment.*—The general treatment of botulism consists of treatment of the digestive tract and stimulation of the nervous system.

Botulinus toxin is a true toxin and differs from the toxins of diphtheria and tetanus in that it is, so far as we know, taken into and possibly produced in the digestive tract and is not altered by the gastric juice. This gives us an opportunity to develop a treatment directed against the toxin in the digestive tract as well as in the blood stream.

Treatment of the digestive tract in cases of botulism has been designed to prevent the further absorption of the toxin by its removal, stimulation of gastric secretions, the use of demulcents and oils. A method of neutralizing the toxin in the digestive tract should also be developed.

**Intestinal Tract:** Treatment of the intestinal tract in cases of botulism cannot be placed on a scientific basis until we know the effect of the intestinal contents on the toxin. Graham has shown that the droppings of chickens suffering from botulism and also droppings found in forage causing botulism when ground up and fed to horses caused death. He apparently assumes that the toxin passed through the intestinal tract of the chickens and that the horses died as the result of the ingestion of this toxin rather than from the production of toxin in the digestive tract following the ingestion of toxin-free organisms. Forssman has shown that the injection of 2,000 lethal doses of toxin in the rabbit intestine does not cause death. He believed that the intestinal contents of the rabbit precipitated the toxin. Until we know whether or not the toxin in the intestinal tract is harmful we must proceed upon the assumption that it is and take steps for its removal, neutralization and the prevention of absorption.

We recommend the use of high enemas that will neutralize the toxin, prevent its absorption and destroy the organisms. We have shown that some of the common ingredients of enemas should be beneficial. Liquid soap neutralizes the toxin, olive oil prevents its absorption and turpentine may have some beneficial action. Iodin and potassium permanganate destroy both the toxin and organisms and might be used to advantage. The effect of soap on the organism is unknown and should be determined. If it can be shown that the toxin in the intestinal tract is harmless and is not produced there, the use of enemas can be restricted to feeding and the control of constipation.

**Stomach:** In those patients in which the symptoms do not appear for several days after the ingestion of the toxic food, we may reasonably assume that there is very little, if any, of the ingested toxin remaining in the digestive tract. But since there is a possibility of infection and production of toxin in the digestive tract, it is necessary to proceed on the assumption that toxin is always present in the stomach of any one suffering from botulism. When the symptoms appear in a



few hours after the ingestion of the poisonous food we should expect to find toxin in the stomach. In these cases paralysis of the stomach apparently sets in early. Case reports show that toxin has been found in the stomach several days after the ingestion of the toxic food.

Treatment of the stomach should have in mind the removal of the toxic contents by stimulation of movement or the stomach pump, the prevention of absorption by the use of demulcents and oils or stimulation of secretions, the neutralization of the toxin and the destruction of the organisms. The removal of the stomach contents is attended with some danger as it may induce pneumonia. The death rate among those vomiting is 75 per cent.; among those not vomiting, 70 per cent. The average time of death of those vomiting is 3.7 days and of those not vomiting 5 days after the ingestion of the toxic food. This indicates that those ingesting the most toxin tend to vomit or the act of vomiting induces a terminal pneumonia.

In our experimental work we have shown that the food taken in with the toxin delays the appearance of the symptoms. This is probably due to a slowing down of the rate of absorption of the toxin. Our work has also shown that a slowing down of the rate of absorption enables a guinea-pig to resist 3 lethal doses of toxin. The use of oils, milk and alcohol slowed down the action of the toxin in the stomach of the rabbit. Iodin, potassium permanganate and liquid soap have a strong neutralizing action on the toxin but it has not been determined whether they can safely be used in the stomach in large enough amounts to be beneficial.

Treatment of the stomach must be begun early, as paralysis of the throat soon sets in and there is great danger of pneumonia. Most of our rabbits dying after the fourth day showed gray hepatization of the lungs. A nonirritating gargle of 2 per cent. argyrol may be used as a precautionary measure.

Throat: Pilocarpin has been used to remove the tenacious mucus usually found in the throat in advanced cases. It "should be used with caution as the patient is unable to cough up fluid from the lungs if pulmonary edema is induced."

Nervous system: Treatment of the nervous system must be general until we know what nerves or nerve centers are affected. Strychnin has been used in most cases.

Supportive measures: The supportive measures in use have been mentioned above.

We cannot hope for a more satisfactory treatment until our knowledge of the subject becomes more exact. With our present knowledge of botulism, the death rate should be reduced when antitoxin becomes more available and the symptoms more readily recognized.

## PROGNOSIS

From an examination of the incomplete statistical data we obtain certain facts which have a bearing on the prognosis. The death rate in this country varies from 60 to 70 per cent. The death rate among those first showing symptoms in all outbreaks in this country is 90 per cent., among those last showing symptoms 60 per cent. The death rate of those vomiting is 75 per cent. Vomiting cannot be considered a favorable sign. The death rate of those showing symptoms in twenty-four hours after the ingestion of the toxic food is 84 per cent.; of those showing symptoms for the first time after seventy-two hours it is 55 per cent., and of those alive after the eighth day it is 20 per cent.

## THE RELATION OF HYPERTHYROIDISM TO DIABETES MELLITUS\*

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At a meeting of the Deutscher Kongress für innere Medizin in 1906, Friedrich Müller<sup>1</sup> suggested that a special type of glycosuria is related to exophthalmic goiter. His immediate reasons for this belief were drawn from his experience with two cases. The first was one of exophthalmic goiter in which he had given thyroïdin, hoping thereby to diminish the size of the thyroid gland. The symptoms of hyperthyroidism did not improve under this form of treatment and sugar began to appear in the urine in increasing amounts. The glycosuria did not diminish after administration of the thyroïdin was stopped, and the patient died in coma a few months later. The second case was that of a woman with a chronic goiter who had taken thyroid extract for a long time, and who had developed diabetes. Some time later the goiter disappeared spontaneously, and, to Müller's surprise, the symptoms of diabetes also disappeared so that the patient was eventually able to take large amounts of carbohydrate without producing glycosuria. These two cases were the basis for Müller's statement that, in the future, the thyroid gland should be studied more carefully in its relation to diabetes.

Since the publication of Müller's paper on this subject, numerous others have appeared in European literature, although but little attention has been paid to it in this country. My purpose is to discuss this topic and to present such data as I have been able to collect from the records of the Massachusetts General Hospital and from the Mayo Clinic.

The earliest report on the relation of the thyroid gland to diabetes was read by Dumontpallier<sup>2</sup> of Paris at a meeting of the Société de Biologie in August, 1867. It is of sufficient historic interest in connection with my paper to deserve a translation:

### EXOPHTHALMIC GOITER AND GLYCOSURIA IN THE SAME PATIENT

A woman, aged 22, complained, according to her family, of chest trouble. Careful examination, however, demonstrated that the lungs were not seriously diseased. The patient was very pale and thin; her eyes were abnormally

\* From the Massachusetts General Hospital, Boston, and the Mayo Clinic.

\* Presented before the Chicago Society of Internal Medicine, Chicago, November, 1920.

1. Müller, F.: Discussion, *Verhandl. d. Cong. f. inn. Med.* **23**:100, 1906.

2. Dumontpallier: *Goître exophtalmique et glycosurie chez la même malade*, *Compt. rend. Soc. de biol.* **4**:116, 1867.

prominent, and her expression was peculiar. The thyroid gland was hypertrophied, especially in the right lobe, and the patient complained of marked pulsation in her heart. The case was undoubtedly one of Basedow's disease, and the condition had been more marked at an earlier date.

Boulimia and excessive thirst had been persistent for several months. The presence of diabetes was suspected, and the urine was examined by Dr. Hardy of Paris, who demonstrated the presence of 62 gm. glucose to the liter of urine. The patient could not accurately estimate the volume of urine excreted in twenty-four hours, but it was considerable, and at night she was often awakened by a desire to urinate.

The prognosis was grave, not on account of the exophthalmic goiter, which is a curable disease and one compatible with life, but on account of the glycosuria which had caused the anemia and great loss of weight.

The patient followed the prescribed treatment for several weeks and showed considerable improvement. Her strength returned; her urine became less abundant, and there was no remission of the Basedow's disease. However, she caught a severe cold in the winter of 1867 and died of an inflammation of the chest.

The existence of these two nervous disorders in the same individual and the development of their principal symptoms is recorded for the benefit of all medicine.

We should add that the etiology in this case is of no less interest than the course of the disease. This young girl developed the first symptoms of exophthalmic goiter a few days after the suppression of her menstruation. The circumstances were as follows: The young woman became overheated at a fête, plunged her arms into a basin of cold spring water and sat down on the damp grass in the shade. The menstruation was stopped by this imprudence and never returned.

These words, twenty-seven years after Basedow's<sup>3</sup> original monograph was published, and seventeen years after Fehling's quantitative method for sugar determination in urine was described,<sup>4</sup> are the first note with regard to this unusual combination of diseases. The first case which appeared in English literature was that of Lauder Brunton<sup>5</sup> in 1874. Hartmann<sup>6</sup> reported two cases from the Tübingen Clinic in 1878. Budde<sup>7</sup> reported two cases in Denmark in 1891, and finally Manges<sup>8</sup> of New York, in 1899, recorded the first case in America. The early papers on this group of cases emphasized the association between two uncommon conditions and did not make any serious effort to inquire into their possible relationship.

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3. Basedow, v. C.: *Exophthalmos durch Hypertrophie des Zellgewebes in der Augenhöhle*, *Wchnschr. f. d. ges. Heilk.* **6**:197, 1840.

4. Fehling, H.: *Ueber die quantitative Bestimmung von Zucker und Starke-mehl mittelst Kuppervitriol*, *Ann. Chem. et Pharm.* **72**:106 1849.

5. Brunton, L.: *Cases of Exophthalmic Goiter*, *St. Barth. Hosp. Rep.* **10**: 255, 1874.

6. Hartmann, C.: *Ueber zwei mit Basedow'scher Krankheit complizirte Fälle von Diabetes mellitus*, *Inaug. Diss. Tübingen*, Fues, 1878.

7. Budde, V.: *Ugesk. f. Læger* **22**:1890. Review in *Neurol. Centralbl.* **10**:112, 1891.

8. Manges, M.: *A Case of Exophthalmic Goiter with Diabetes Mellitus and Pigmentation*, *Mt. Sinai Hosp. Rep.* **2**:59, 1899.

In 1909 Sattler<sup>9</sup> made a more elaborate study of the subject. He collected fifty-six reported cases, thirty-seven of which had been followed for a time sufficient to afford positive information. Twenty-five of these ended fatally in a comparatively short time; seven patients died in coma. In the majority of cases the diabetes developed after a pre-existent exophthalmic goiter, although in a few the diabetes seemed to antedate the thyroid disturbance. There seemed to be a certain hereditary influence in several so that Sattler commented on the frequency with which one or the other disease occurred in various members of the same family. None received surgical treatment.

Recently, more and more speculation as to the reason for the coincidence between these diseases has developed. Certain observers believe that it is purely by chance that the two are found together. Others argue that since thyroid extract can produce alimentary glycosuria in various normal persons and can exaggerate an alimentary glycosuria in almost all persons with hyperthyroidism, the relationship between diabetes and hyperthyroidism is closer. Finally Falta,<sup>10</sup> by fathering the school of endocrinologists, stimulated an immense amount of clinical and experimental work on the interrelationship of the various ductless glands.

It is not my purpose to attempt to analyze the evidence in favor of and against the interdependence of the thyroid, the pancreas and the suprarenals in diabetes and hyperthyroidism. The fact remains that the two diseases occur together at times, whether by chance, or because over-activity of the thyroid stimulates metabolism and eventually fatigues the pancreas until diabetes develops in predisposed persons, or through a physicochemic reaction between the internal secretions of the thyroid and pancreas.

Suggestions have been made that the peculiar characteristics of the thyroid gland may be used for therapeutic purposes in the management of diabetes. Falta<sup>11</sup> reported three cases of exophthalmic goiter and diabetes in which the patients were treated by roentgen-ray exposure of the thyroid gland. Two patients derived no apparent effect. The third patient, who excreted about 15 gm. dextrose after a diet containing 80 gm. carbohydrate, appeared to improve after one roentgen-ray treatment. The urine cleared up and remained sugar-free, even when a more liberal diet was eaten; the patient gained weight and the symptoms of thyroid tumor and diabetes disappeared so that the man

9. Sattler: *Die Basedow'sche Krankheit*, Leipzig, Engelmann 1:384, 1909.

10. Falta, W.: *The Ductless Glandular Diseases*, Philadelphia, Blakiston, 1916, pp. 674.

11. Falta, W.: *Ueber Glykosurie und Fettstühle bei Morbus Basedowii; zugleich ein Beitrag zur Röntgentherapie dieser Krankheit*, *Ztschr. f. klin. Med.* 71:1-22, 1910.

was considered normal when he was discharged from the hospital. Crile<sup>12</sup> operated on a man, aged 42, with diabetes whose urinary sugar averaged 95 gm. each day before operation. The left and right cervical sympathetic nerves were resected, the left suprarenal was removed and a partial thyroidectomy performed. Four months later the patient had gained 9 pounds in weight and was remaining aglycosuric on a diet containing 250 gm. carbohydrate. O'Day<sup>13</sup> treated four patients with exophthalmic goiter and diabetes. The first was a man, aged 24, who was thyroidectomized after preliminary hot water injections into the gland substance. His recovery was surprisingly rapid and within a short time his diet was unrestricted and his urine remained sugar-free, even when he ate candy. O'Day's other patients were handled in similar manner and recovered a practically normal carbohydrate tolerance. Rhodenburg's<sup>14</sup> two observations are nearly identical. He described one interesting case in which the father, mother, and one maternal aunt were diabetic, the patient himself developing the disease at the age of 18. The four members of the family were given thyroid extract at intervals which repeatedly caused a marked increase in sugar excretion in all. Finally, the man in question developed symptoms suggesting exophthalmic goiter and a portion of his thyroid gland was removed. About six months after the operation his urine was sugar-free, even after three ice cream sodas taken within twelve hours. Rhodenburg's second case was that of a woman, aged 53, who developed symptoms of excessive thyroid activity in 1915 and diabetes in 1919. Three months after thyroidectomy she had gained 35 pounds and her urine remained sugar-free with an unrestricted diet.

On the whole, so far as may be judged from the literature, a possible relationship between hyperthyroidism and diabetes has been recognized for a long time. The combination is relatively uncommon but is serious. Many theories as to the cause of such intimate association between these two diseases of metabolism have been brought forward, although at present the evidence is so conflicting as to be inconclusive. Attempts have been made to treat diabetes through the thyroid gland, and a few cases have been reported in which, when the thyroid tumor disappeared, either spontaneously, by roentgen-ray exposure, or by operative interference, the diabetes improved in striking fashion and possibly was cured.

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12. Crile, G. W.: *The Kinetic Drive; Its Phenomena and Its Control*, J. A. M. A. **65**:2129 (Dec. 18) 1915.

13. O'Day, J. C.: *Carbohydrate Tolerance in Hyperthyroidism*, Surg., Gynec. & Obst. **22**:206, 1916. *Diabetes in Association with Toxic Goiter*, New York M. J. **111**:815, 1920.

14. Rohdenburg, G. L.: *Thyroid Diabetes*, *Endocrinology* **4**:63, 1920.

The material presented in this paper consists of thirty-nine hitherto unreported cases of diabetes complicated by thyroid disease. Thirty-three of the patients were observed in the Mayo Clinic and six in the Massachusetts General Hospital. A number of cases of thyroid disease and mild glycosuria were observed in both institutions but were excluded from this series on the ground that the relation between transitory glycosuria in thyroid disease and true diabetes has not been established.

The combination of exophthalmic goiter and diabetes is no more common in America than in Europe. Billings<sup>15</sup> found one case of glycosuria in a series of sixty-one cases of exophthalmic goiter in Chicago; Greeley<sup>16</sup> found six cases of exophthalmic goiter in 614 cases of diabetes at Waukesha, and in the Mayo Clinic records there were only nine cases of diabetes among the 1,800 cases of exophthalmic goiter which were reviewed for this paper. Possibly these two diseases occur together more frequently along the eastern sea border than in the Middle West, since Thompson<sup>17</sup> reported three cases of diabetes among eighty cases of exophthalmic goiter in New York and there were four diabetic patients among 315 with exophthalmic goiter and hyperthyroidism at the Massachusetts General Hospital.

A statistical review of the cases in this series does not add anything to Sattler's work. The age, sex and type of cases were much the same as his. Three of the four nonoperated patients with thyroid toxemia whose histories were followed for a reasonable length of time died within a few months after the diabetes was first apparent. Of the twenty-two cases, including hyperthyroidism due to exophthalmic goiter and adenoma, only one was known to be diabetic before the thyroid symptoms supervened, although in a few, as in Sattler's series, it was impossible to differentiate the symptoms of the two diseases. An hereditary influence was suggested in two cases; one patient's mother died of diabetes and another patient's mother and brother died of diabetes.

The main interest in the cases of this series lies in the fact that they made it possible to follow the effect of thyroid operations on the course of diabetes in a few more cases than had been published. Only those cases are included for this study which were followed until death or long enough to avoid apparent immediate results which were not true. The material is tabulated in Tables 1, 2, 3 and 4.

15. Billings, F.: Symposium on Exophthalmic Goiter. *J. A. M. A.* **48**:349 (Jan. 26) 1907.

16. Greeley, H. P.: Focal Infections and Their Relation to Diabetes, *Wisconsin M. J.* **14**:464, 1915.

17. Thompson, W. G.: Exophthalmic Goiter. A Clinical Study of Eighty Cases, *Tr. Assn. Am. Phys.* **21**:502 1906.

In Table 1 are tabulated the findings in five cases of diabetes associated with nontoxic thyroid enlargement. These cases seem fairly representative of ordinary diabetes. Three patients died in typical fashion, one of pulmonary tuberculosis, one after a surgical operation

TABLE 1.—NONTOXIC THYROID DISEASE AND DIABETES—NONOPERATED CASES

Case, Age, Sex	Duration of Goiter Sym- ptoms	Duration of Diabetic Sym- ptoms	Glycosuria		Maxi- mum Weight, Pounds	Present Weight, Pounds	Date	Remarks
			Per Cent.	24-Hr. Amount Sugar, Gm.				
1 51, M	2 yrs.	18 mos.	6.0	224	220	162	1/ 5/10 1/31/14	Died of diabetes
2 32, F	10 yrs.	2 mos.	6.0	102	100	95	5/29/17 1/13/19	Losing weight and strength rapidly despite treatment*
3 67, F	Since a girl	Not known	3.5- 7.0	—	—	—	10/ 7/14	Died shortly after operation for cancer of the uterus
4 49, F	35 yrs.	7 yrs.	3.0	36 none	170	170 161	6/15/18 8/ 2/20	B.M.R.—17 B.M.R.—9; has been dieting carefully since last entry
5 47, M	13 yrs	4 yrs.	—	450	—	—	4/ 3/11 5/ 3/11	Death; necropsy showed pulmonary tuberculosis

\* Patient died June 5, 1918.

TABLE 2.—NONTOXIC THYROID DISEASE AND DIABETES—OPERATED CASES

Case, Age, Sex	Duration of Goiter Sym- ptoms	Duration of Diabetic Sym- ptoms	Glycosuria		Maxi- mum Weight, Pounds	Present Weight, Pounds	Date	Remarks
			Per Cent.	24-Hr. Amount Sugar, Gm.				
1 57, F	Since a child	Not re- corded	4.0	80	159	115	8/25/19 9/12/19 3/22/20	Partial thyroidectomy Living on strict diet; keeps sugar free except for trace occasionally
2 53, F	32 yrs.	8 mos.	5.0- 3.0	170 140	200 ...	148 ...	5/15/19 5/31/19 3/22/20	Partial thyroidectomy Feels fairly well; diabetes unimproved
3 55, F	26 yrs.	Not re- corded	7.0 1.2	84 ...	160 ...	152 150	5/ 5/15 8/ 8/15 3/15/20	Partial thyroidectomy Is restricting diet to best of ability; diabetes unimproved
4 54, F	30 yrs.	6 mos.	2.0 4.5	32 44	199 ...	182 189	7/22/19 8/13/10 3/18/20	Partial thyroidectomy Diabetes unimproved

on the uterus, and one, a man, aged 51, after six years' illness. One woman, (Case 2), aged 32, had a rather acute diabetes but there was no evidence for believing that the thyroid enlargement accelerated its course. Case 4 is the most interesting of this group. The patient had



diabetes with moderate hypothyroidism. The diminished metabolism did not increase the sugar tolerance because it was no lower when the metabolic rate was more nearly normal. These cases suggest that nontoxic thyroid disease does not affect diabetes.

In Table 2 are tabulated the findings in four cases similar to those described in Table 1. The patients were all elderly persons with mild diabetes. They had had partial thyroidectomies without cure of the diabetes, nor was it obviously affected. These cases, therefore, suggest that thyroidectomy alone is a valueless therapeutic measure in diabetes.

TABLE 3.—TOXIC THYROID DISEASE AND DIABETES—NONOPERATED CASES

Case, Age, Sex	Type of Goiter	Duration of Goiter Symptoms	Duration of Diabetic Symptoms	Glycosuria		Maximum Weight, Pounds	Present Weight, Pounds	Date	Remarks
				Per Cent.	24-Hr. Amount Sugar, Gm.				
1 40, F	Exophthalmic	8 mos.	2-3 mos.	4.0	—	115	102	11/18/16 11/28/16	Died suddenly; necropsy showed persistent thymus
2 19, F	Exophthalmic	1 yr.	Not present	—	—	—	129	1/1/09	Feeling fairly well; still has exophthalmic goiter. Developed acute diabetes; running down hill rapidly; end result unknown
			Not present	—	—	—	123	4/20/11	
			4 mos.	—	450	—	87	10/8/12	
3 30, F	Exophthalmic	7 yrs.	2 mos.	— 3.6	161 —	—	—	7/9/14 9/29/15	Died of diabetes

In Table 3 are tabulated data from three cases of exophthalmic goiter complicated by diabetes, in which operations were not performed. This material is small but noteworthy. The three goiter cases are not unlike Dumontpallier's original case in the rapidity of their course. Case 2 is especially interesting since the patient did not develop diabetes until she had had a goiter for at least two years. Finally, the diabetes became extremely acute. These cases suggest that patients with exophthalmic goiter, because of their high metabolism, burn themselves up quickly if diabetes develops, although more detailed information on the relation of the metabolic rate to prognosis of the diabetes in the various types of goiter is highly desirable. In any event these cases of true exophthalmic goiter accompanied by diabetes emphasize the gravity of the condition.

Table 4 represents the results in nine cases of exophthalmic goiter and toxic adenoma in which operation was performed. These cases are all interesting individually. In Case 1 the patient did not have diabetes until after the thyroid vessels had been ligated. Although

TABLE 4.—TOXIC THYROID DISEASE AND DIABETES—OPERATED CASES

Case, Age, Sex	Type of Goiter	Duration of Goiter Symptoms	Duration of Diabetic Symptoms	Glycosuria		Maximum Weight, Pounds	Present Weight, Pounds	Date	Operation and Remarks
				Per Cent.	24-Hr. Amount Sugar, Gm.				
1 41, M	Exophthalmic	2 yrs.	Not present	—	—	175	142	6/15/16	Hot water injection Ligation of thyroid vessels At first improvement after operation, then rapid downward course Death
			Acute onset	9.0	180	...	116	7/5/16 7/10/16 7/14/16 9/9/16	
								1/2/17	
2 3, M	Exophthalmic	3 mos.	Not recorded	Trace	Trace	130	115	10/12/15 10/16/15 10/21/15	Ligation of thyroid vessels Right lobe and isthmus extirpated Dieting strictly Had two roentgen-ray treatments Losing rapidly
				2.0	...	...	119	12/14/15	
			No symptoms	None	None	...	115	9/8/16	
				...	...	...	124	10/4/16	
			3 mos.	3.0	54	...	101	6/29/18	
3 47, F	Exophthalmic	9 yrs.	3 mos.	2.5	160	140	95	10/6/14 11/19/14	Ligation of thyroid vessel Right lobe, isthmus and part of left lobe extirpated Death
								11/24/14	
								11/27/14	
4 47, F	Exophthalmic	1½ yrs.	Not recorded	2.0	37	165	122	1/30/14 2/12/14	Ligation of thyroid vessels Right lobe, isthmus and ½ left lobe extirpated Dieting; sugar now in urine every day Died of diabetes and pneumonia
								2/17/14	
								7/12/19	
								12/22/19	
5 44, M	Exophthalmic	8 mos.	1 yr.	1.4	12	170	170	7/15/15	On strict diabetic diet Ligation of thyroid vessels Patient returned Extirpation of right lobe and isthmus Urine has no sugar; patient not dieting
								1/22/15 1/29/15	
				1.0	—	...	177	5/8/15 5/14/15	
								3/15/20	
6 57, F	Adenoma	7 yrs.	1 yr.	4.0	72	170	130	5/7/18 6/14/18	Partial thyroidectomy Not dieting; feeling well; no glycosuria Not dieting; feeling well; trace of sugar
							145	3/20/20	
							152	11/19/20	
7 53, F	Adenoma	40 yrs.	6 yrs.	4.0	80	180	154	10/12/17 11/30/17	Partial thyroidectomy Not dieting; feeling well; no glycosuria
							165	3/20/20	
8 52, F	Adenoma	Years	1½ yrs.	4.0	80	110	140	3/8/16 5/20/16 6/4/19	Partial thyroidectomy* Tonsillectomy Has regained weight and strength; urine sugar free except when she overeats of starchy foods
								11/16/20	
9 56, F	Adenoma	40 yrs.	9 yrs.	3.0	30	160	130	9/5/19 10/1/19	Partial thyroidectomy Died of bronchopneumonia

\* I am obliged to Dr. George Kessel of Cresco, Iowa, who performed the operations quoted in this case and who has given me the subsequent information.

the patient improved subjectively, the operation did not prevent the development of diabetes and the patient died after a short course. In Case 2, the patient had a trace of sugar on first observation, but no diabetic symptoms. However, his mother and one brother died of diabetes, so possibly there was an inherited tendency toward the disease. The treatment consisted in ligation of the thyroid vessels, partial thyroidectomy, strict diet, and roentgen-ray exposure of the thyroid remnant. Such thorough treatment did not affect the course of the diabetes. In Case 3 the patient, a woman, died immediately after operation. In Case 4, the patient had a ligation of the thyroid vessels; the right lobe, isthmus and five-sixths of the left lobe of the thyroid were extirpated. Moreover, the patient dieted strictly. In spite of this treatment she was still a diabetic when she died, although she lived for nearly six years after she was first examined and did not develop acute diabetes as in the other cases. In Case 5 the patient had the mildest type of diabetes of the series. He improved after operation and had no sugar on an unrestricted diet five years after he was first examined. This patient was a true diabetic and had been under treatment before he developed exophthalmic goiter. The superimposed thyroid toxemia did not seem to affect the diabetes especially; therefore, it is difficult to be convinced that the thyroid operation was the only cause of the apparent improvement in the diabetes. Cases 6, 7 and 8 are more suggestive of the cases described by O'Day and Rohdenburg. The patients had toxic adenoma and partial thyroidectomy on this account. The patient in Case 6 had gained 22 pounds two and one half years after operation, was feeling well, was not dieting, and the urine contained only a trace of sugar. The patient in Case 7 had almost an identical result from the operation. Two and one-half years later she had gained back twenty-two pounds of weight and was feeling well. The patient in Case 8, four and one half years after operation, was reported to have regained her weight and strength and to be aglycosuric most of the time. The patient in Case 9 developed bronchopneumonia after partial thyroidectomy and died.

On the whole, the results of operation on the thyroid gland of diabetic patients with hyperthyroidism in this small number of cases were not particularly encouraging. However, Cases 4, 5, 6 and 7 suggest that occasionally an operation may not only prolong life but may even be of greater benefit.

The series is too small to afford conclusive evidence with regard to the advisability of operation in this type of case. However five patients with nontoxic goiter were operated on with no mortality, six with toxic adenoma with one death, and six with exophthalmic goiter with one death. Therefore, it does not seem overradical to advise operation for properly selected and prepared patients in this group of cases, since

the risk does not seem out of proportion to the possible benefit to be gained, and since the prognosis is otherwise very grave.

Obviously my observations are too fragmentary to warrant any definite conclusions and I can only draw attention to certain features with regard to the relationship between thyroid disease and diabetes.

Hyperthyroidism and diabetes occur together in the same person in a small number of cases. There is no established evidence that such coincidence is more than chance.

The diabetes usually follows the thyroid disturbance, but may precede it, and tends to parallel in severity the severity of the thyroid intoxication.

There is no reason for assuming that partial thyroidectomy alone has any curative effect on diabetes as the patients in this series with nontoxic goiter who were operated on showed no improvement of the diabetes.

Certain patients with toxic thyroid disease and diabetes, on the other hand, improve to a considerable degree after the thyroid symptoms are checked. This probably occurs because of a change in the rate of metabolism and not because a portion of the thyroid gland has been made functionless. Before this supposition can be established more accurate information must be obtained with regard to the effect of an increased rate of total metabolism from thyroid intoxication on the carbohydrate metabolism of diabetics.

# THE OCCURRENCE OF ABNORMAL LEUKOCYTES IN THE BLOOD IN ACUTE INFECTIONS

ACUTE BENIGN LYMPHOBLASTOSIS

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During the past year we have had several acute infectious cases, running a febrile course, usually mild and all ending in recovery, but in which the blood picture gave rise to considerable apprehension, at the time, as to the ultimate outcome.

The appearance in the blood of cells indistinguishable from those found in acute leukemia, together with enlargement of the lymph nodes and sometimes enlargement of the spleen, with a moderate fever, and absence of definite signs pointing to other disease entity, is a clinical picture that might easily give rise to a grave prognosis.

An excessive proportion of lymphocytes, a reversal of the polymorphonuclear lymphocyte relation, is not infrequently seen in the normal blood of children, and occasionally in adults under pathologic conditions other than lymphatic leukemia. A lymphocytosis is also noted in some cases following the administration of certain therapeutic agents. In early childhood is found the most marked increase, due to congenital syphilis, cholera infantum, rickets, scurvy and pertussis. In adult life, hemophilia, cervical adenitis, enlarged tonsils, chlorosis, pellagra, exophthalmic goiter, varicella, mumps, secondary anemia associated with syphilis, tuberculosis and malaria frequently show an excessive percentage of lymphocytes in the blood. This condition is also noted at times following the administration of therapeutic doses of thyroid extract, tuberculin, pilocarpin, and quinin hydrochlorate subcutaneously.

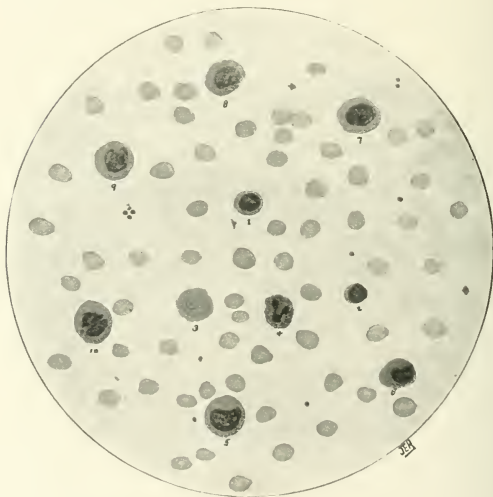
However, the cases presented in this series have a different aspect and clinical picture from the type of cases noted above. They also present a different picture from that found in acute leukemia, and while each new case may give rise to grave doubts as to prognosis, a careful investigation and study of the history and findings will usually serve to distinguish this type of case from true leukemia.

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\* From the Division of Clinical Medicine of the U. S. Naval Hospital.

Whether or not these cases represent a distinct disease entity may, perhaps, be questioned, but the term "acute benign lymphoblastosis" is suggested as covering the essential features of this disease.

The symptoms, physical findings and course of the disease, in themselves, are not alarming, but when viewed in conjunction with the blood findings the case presents a rather distinct and often startling picture.



Composite blood picture drawn to show type of lymphoblast encountered in "acute benign lymphoblastosis." 1 and 2, large and small lymphocyte commonly seen in normal blood; 3, large mononuclear cell (endotheliocyte); 4, polymorphonuclear neutrophil; 5, 6, 7, 8 and 9, types of lymphoblasts encountered in "acute benign lymphoblastosis," rarely seen in normal blood; 10, Rieder type of lymphoblast.

#### REPORT OF CASES

CASE 1.—White male; aged 19; unmarried.

*Complaint.*—Cough, general malaise, soreness in upper respiratory passages.

*Family History.*—Negative.

*Personal History.*—Smallpox and measles in childhood; influenza in 1918, duration two weeks, good recovery; occasional attacks of tonsillitis during past five years.

*Present Illness.*—The patient had been feeling badly for about one week prior to admission to hospital. He had headaches, slight cough and lassitude.

*Physical Examination.*—On admission, temperature, 103.8 F.; pulse, 104; respiration, 22. The patient was well nourished, with a fair amount of subcutaneous fat. The color of the skin and mucous membranes was good; no petechiae. Glands in neck, anterior, posterior and submaxillary, were enlarged, as were those in the axillae and groins. They were discrete and mobile. Those in the groin were particularly prominent, filling Scarpa's triangle and extending upward along Poupart's ligament nearly to the anterior superior spine. Pupils were equal and reacted to light and accommodation. Tongue thick, red and somewhat velvety. Tonsils were large and there was some angina; pharynx moderately congested; teeth extensively filled, but otherwise good. There was a faint systolic murmur at left second interspace, otherwise heart was negative. Lungs showed a few scattered râles, inconstant in distribution.

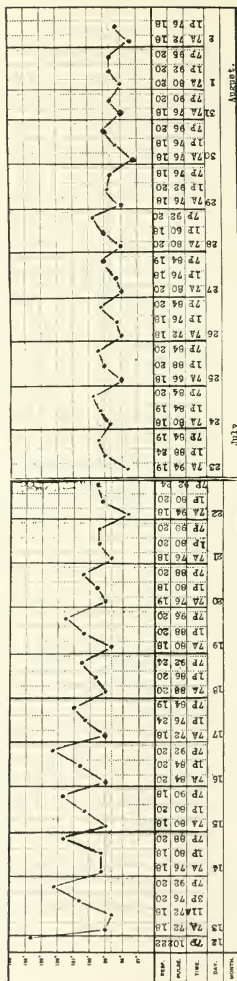
TABLE 1.—BLOOD CHART OF CASE 1

Date, 1929	Leukocytes, per C.Mm.	Polymorphonuclear neutrophils, %		Lymphocytes (all sizes), %		Mononuclears, %	Transitionals, %	Eosinophils, %	Mast Cells, %	Myelocytes, %	Rieder Type Lym- phoblast, %	Unclassified Leuko- cytes, %	Erythrocytes, per C.Mm.	Hemoglobin, %	Remarks
7/18	30,000	15	84	0	0	0	0	0	0	1	0	0	4,200,000	78	
7/19	34,000	12	87	0	0	0	0	0	0	0.5	0	0.5	.....	..	Rieder cell (.)
7/22	24,000	8	89	0	0	0	0	0	0	3	0	0	.....	..	Widal negative
7/26	14,000	14	84	0	0	0	0	0	0	1	0	2	.....	..	Blood culture neg.
7/29	11,200	13	86	0	0	0	0	1	0	1	?	0	.....	..	Throat smear: fusos- spirillary (Vincent's) organisms
8/ 2	9,500	10	86	0	0	0	0	3	1	0	?	0	.....	..	Wassermann neg.
8/ 5	7,800	30	69	0	0	0	0	1	0	0	0	0	.....	..	Rieder cells
8/12	7,500	37	58	0.5	0	3.5	0.5	0	0.5	0	0.5	0.5	.....	..	Coagulation time, 4 minutes
8/18	6,200	34	58	0	0	6	0.5	0	0	0	0.5	0	.....	..	
8/23	9,000	35	57	1	0	6.5	0.5	0	0.5	0	0.5	0	4,400,000	85	Feces negative for ova and parasites
9/ 4	5,500	38	55	1	2	4	0	0	0	0	0	0	4,880,000	95	No abnormal cells seen
9/29	6,200	63	34	0.5	0.5	1	0	0	0	0	0	0	5,400,000	100	
10/ 2	7,100	57	39	0.5	0.5	1	1	0	0	0	0	0	.....	..	

Abdomen appeared to be full and tense; liver not enlarged; spleen not palpable but appeared enlarged to percussion; no tenderness; no tumors. Bones of limbs showed no swelling or tender areas. Reflexes, both superficial and deep, were normal. Eye grounds negative.

*Laboratory Data.*—Urine showed a trace of albumin and an occasional hyalin cast. Sputum showed no tubercle bacilli. Numerous streptococci, fusiform bacilli and spirillae were present in sputum. Throat cultures negative for Klebs-Loeffer bacilli. Smears from the throat showed the presence of Vincent's organisms during the acute stage of the disease. The blood was negative for malarial parasites and repeated blood cultures during the course of the disease were negative. The Noguchi reaction was negative. The Widal test was negative. Stools normal and negative for ova or parasites. The coagulation time of the blood was four minutes. The complete record of the blood examinations is shown in Table 1.

The character of the blood picture and the type of cell present were fairly constant in all the cases and will be described later in the report.



Pulse, respiration and temperature record in Case 1.



*Clinical Course.*—Patient continued to run a febrile course, temperature varying from 99 F. in the morning to 102 F. in the evening during the first week. During the second week the temperature gradually approximated normal and the patient was up and about at the end of the second week. The type of temperature chart in all these cases was very similar and usually after running a more or less continuous course for three or four days the fever became remittant, gradually approaching normal but with the tendency to slight evening rise during the second week. A section of the temperature chart in Case 1 is reproduced as being fairly characteristic of this disease. On the fifth day, the patient developed a superficial ulcer about the right nares which healed after ten days. The glandular enlargement gradually subsided. Six weeks following admission, the glands were still slightly enlarged but discrete and mobile. The increase in the lymphocytic cells persisted for several weeks after the temperature was normal and after the patient was free from all symptoms. Recovery was uneventful and patient has been pursuing his usual duties since discharge from hospital.

CASE 2.—White male; aged 20; unmarried.

*Complaint.*—Sore throat, swelling of glands of neck, and general malaise.

*Family History.*—Negative.

*Personal History.*—Measles, whooping cough and chickenpox in childhood. Occasional attacks of tonsillitis for past three years.

TABLE 2.—BLOOD CHART OF CASE 2

Date, 1920	Leukocytes, per C. Min.	Polymorphonuclear neutrophils, %		Lymphocytes (all sizes), %		Mononuclears, %		Transitionals, %		Eosinophils, %	Mast Cells, %	Myelocytes, %	Rieder Type Lym- phoblast, %	Unclassified Lenko- cytes, %	Erythrocytes, per C. Min.	Hemoglobin, %	Remarks
10/18	9,100	26	71	1	2	0	0	0	0	0	0	0	0	0	4,700,000	90	Throat culture negative for Klebs-Loeffer bacilli
10/19	12,600	19	70.5	0	0	0	0	0	0	0	0	0	0.5	0	.....	..	Throat smears: fusospirillary (Vincent's) organisms
10/20	11,400	32	67	0.5	0	0.5	0	0.5	1	0	0	0	0	0	.....	..	
10/21	9,800	43.5	56	0	0.5	1	0	0	0	0	0	0	0	0	.....	..	
10/22	7,200	29	69	0.5	0.5	0.5	0	0.5	0	0	0.5	0	0	0	.....	..	
10/24	7,100	51	48	0	1	0	0	0	0	0	0	0	0	0	.....	..	Rieder cell
10/25	7,200	38	59	1	1	0.5	0	0	0	0.5	0	0	0.5	0	.....	..	
10/27	6,400	49	50	0	0	1	0	0	0	0	0	0	0	0	.....	..	
10/29	7,600	64	32	2	0	0	0	0	0	0	0	0	0	0	.....	..	
12/ 1	7,000	71	25	2	0.5	0.5	0	0	0	0	0	0	0	0	5,200,000	100	

*Present Illness.*—Patient has had headaches and throat has been sore for about one week. During this period he noticed swelling in glands of neck, which gradually increased up to the time of his admission to hospital.

*Physical Examination.*—On admission, temperature, 99 F.; pulse, 82; respiration, 20. Patient was well nourished and muscular. The color of the skin and mucous membranes was normal. There were no hemorrhagic areas. The glands of the neck, anterior, posterior and submaxillary, were greatly enlarged, so that the patient had difficulty in wearing collar. There was practically no tenderness and glands were not adherent or matted together. The glands in the groins and axillae were slightly enlarged. The epitrochlears were not palpable. Pupils were equal and reacted normally. Tonsils were hypertrophied and rather marked angina was present. There was a small ulcer over left tonsil covered with a grayish exudate. Teeth negative. Reflexes, both super-

ficial and deep, were normal. Lungs were clear and heart negative. Spleen not palpable and not enlarged to percussion.

*Laboratory Data.*—Throat cultures were negative for Klebs-Loeffler bacilli. Roentgenogram of chest showed hila shadows somewhat enlarged, more so on the right; bronchial trunks slightly more prominent than normal. No evidence of tuberculosis. Urinalysis negative. Smears from throat showed the presence of the organism of Vincent's angina. Blood negative for malarial parasites and blood cultures taken at various times during the course of the disease were negative. Stools negative for ova or parasites. The complete record of the blood examinations is shown in Table 2.

*Clinical Course.*—Patient ran a mild febrile course with tendency to evening elevation to 99.6 F. The angina gradually subsided and the glandular enlargement slowly disappeared. At the end of the twelfth day temperature remained normal and patient was up and about. Recovery was uneventful. Two months following discharge the glands of neck were still palpable but there was no visible enlargement of the neck. Glands of the groins and axillae normal. The blood picture in this case, as in the others of this series, showed a tendency to return to normal more slowly than the temperature, and abnormal cells could be found in the smears after patient was clinically well. The marked enlargement of the cervical lymph glands in this case raised the question of Hodgkin's disease, which, however, could be definitely ruled

TABLE 3—BLOOD CHART OF CASE 3

Date, 1920	Leukocytes, per C.Mm.	Polymorphonuclear neutrophils, %	Lymphocytes (all sizes), %	Mononuclears, %	Transitionals, %	Eosinophils, %	Mast Cells, %	Myelocytes, %	Rieder Type Lym- phoblast, %	Unclassified Leuko- cytes, %	Erythrocytes, per C.Mm.	Hemoglobin, %	Remarks
11/2	20,100	24	74	0	0	0	1	0	0.5	0.5	.....	..	Throat culture negative for Klebs-Loeffler bacilli
11/3	20,200	22	76	1	1	0	0	0	0	0	.....	..	Throat smears: fusospirillary (Vincent's) organisms
11/8	14,400	36	60	0.5	1	1.5	0	0	1	0			
12/2	7,000	38	54.5	2	3	3	0.5	0	0.5	0	4,600,000	95	Rieder cell

out by the character of the enlargement, the blood picture and the clinical course. Since discharge from hospital patient has been pursuing his usual duties and feels entirely well.

CASE 3.—White male; aged 20; unmarried.

*Complaint.*—Sore throat, headaches and general malaise.

*Family History.*—Negative.

*Personal History.*—Mumps and tonsillitis in childhood; influenza in 1917, incapacitated one week, good recovery; furunculosis in 1918, duration ten days, no recurrence since; otitis media in October, 1920, which subsided in one week.

*Present Illness.*—Began rather suddenly with sore throat, loss of appetite, and feeling of lassitude. These symptoms gradually became more marked up to time patient was admitted to hospital.

*Physical Examination.*—On admission, temperature, 103.4 F.; pulse, 96; respiration, 22. Patient was well nourished and muscular. Skin and mucous membranes normal. No hemorrhagic areas. Glands in neck, both anterior and posterior, slightly enlarged and tender. Glands of axillae and groin not

enlarged. Tonsils hypertrophied and covered with follicular exudate. Pupils are equal and react normally. Heart and lungs negative. Abdomen slightly distended; no tender areas; no evidence of tumors. Spleen not palpable but enlarged to percussion. Liver not enlarged. Reflexes, both superficial and deep, are normal. Eye grounds negative.

*Laboratory Data.*—Throat cultures negative for Klebs-Loeffler bacilli. Smears from throat show presence of organisms of Vincent's angina. Blood was negative for malarial parasites and blood cultures all negative. The Noguchi reaction was negative. Stools normal and negative for ova and parasites. The sputum was negative for tubercle bacilli. Urine showed slight traces of albumin, otherwise negative. The complete record of the blood examinations is shown in Table 3.

*Clinical Course.*—Patient ran a continuous temperature for four days, following which the temperature became remittent, being normal in the morning and approximating 100 F. in the evening. At the end of the thirteenth day, the temperature remained normal, and the patient felt entirely well. The angina gradually subsided but the glandular enlargement of the neck persisted for several weeks. Recovery was uneventful, and the patient has been pursuing his usual duties since discharge from hospital and feels entirely well.

TABLE 4.—BLOOD CHART OF CASE 4

Date, 1920	Leukocytes, per C.Mm.	Polymorphonuclear neutrophils, %	Lymphocytes (all sizes), %	Mononuclears, %	Transitionals, %	Eosinophils, %	Mast Cells, %	Myelocytes, %	Reider Type Lym- phoblast, %	Unclassified Leuko- cytes, %	Erythrocytes, per C.Mm.	Hemoglobin, %	Remarks
11/6	6,000	46	51	0	2	0	0.5	0	0.5	0			
11/7	6,200	51	48	1	0	0	0	0	0	0			
11/9	6,400	43	53	3	2	1	1	0	0	0			
12/6	7,200	53	39	2	1.5	1.5	2	0	0	1	5,330 (90)	100	

CASE 4.—White male; aged 19; unmarried.

*Complaint.*—Headache, general malaise and acute coryza.

*Family History.*—Negative.

*Personal History.*—Measles and mumps in childhood; acute enteritis in December, 1919; good recovery.

*Present Illness.*—About four days prior to admission patient had been having rather severe headaches and coryza, which gradually increased in intensity up to time of admission to hospital.

*Physical Examination.*—On admission, temperature, 100.6 F.; pulse, 84; respiration, 20. Patient was well nourished and showed no evidence of recent loss of weight. Color of skin and mucous membranes was normal and there were no hemorrhagic spots. Glands of neck showed slight enlargement but no tenderness; glands of groins and axillae not enlarged. Pupils are equal and react normally. Reflexes, both superficial and deep, are normal. Lungs show a few scattered râles more marked at both bases. Patient has an acute coryza with a rather free mucopurulent discharge from the nose. Heart negative; abdomen slightly distended and somewhat tender in lower left quadrant. There was evidence of accumulation of feces in sigmoid and descending colon; spleen was not palpable; liver not enlarged.

*Laboratory Data.*—Cultures from throat were negative for Klebs-Loeffler bacilli. Blood negative for malarial parasites and blood cultures all negative. Stools show no ova or parasites. Sputum negative for tubercle bacilli. Urine negative. Roentgenogram of chest entirely negative. The complete record of blood examinations is shown in Table 4.

*Clinical Course.*—Patient ran a continuous temperature for five days following which temperature became remittent and remained normal after ninth day. The abdominal tenderness disappeared following a copious enema. The blood picture gradually approximated normal and one month following discharge no abnormal cells were found. Recovery was uneventful and patient has been pursuing his usual duties since discharge from hospital and feels entirely well.

#### DISCUSSION

The blood picture is essentially the same in all of these cases; the leukocytosis, when present, seemed to be due to an increase in the lymphadenoid cells. These pathologic lymphocytes differ from the cells seen in lymphatic leukemia, in that they do not show the poor staining reaction of the cytoplasm and nucleus seen in that condition. No degenerated cells were observed in this series such as are frequently found in the acute leukemias. The heavy staining nuclei of the lymphoblast in this disease may be placed centrally or eccentrically; it is often round, oval, or irregular in outline, showing deep indentations and occasionally showing the clover-leaf or bilobed Rieder type nucleus. Occasionally, azure granules were noted in the cytoplasm and vacuoles in the dark opaque blue were not infrequently noted. None of these cells showed an oxidase ferment, thus differing from those of myelocytic origin. They are evidently the result of stimulation of lymphadenoid tissue rather than of bone marrow.

In this group we find cells of a distinctly pathologic type corresponding to the germinal center type of lymphoblast. Every gradation in size, from small lymphocytes corresponding in size to the red cell, to a type of cell distinctly larger than the mononuclear-transitional variety, often three times the diameter of the red cells, were noted. No effort is made to differentiate between the large and small cells in making the differential count, as such attempt would be futile.

The small lymphocyte, as a rule, stained normally with Wright's and Wilson's stain, but the majority of cells making up this group consist of large lymphadenoid cells with a protoplasm so darkly stained that it is at first difficult to distinguish them from myelocytes. Indeed, in some cases when hints of a granular appearance are noted in the darkly stained cytoplasm, we find it impossible to be sure whether we are dealing with a large lymphocyte or a myelocyte, except by special staining methods.

These cells have been described by Engel as "mononuclear cells" and by Weil as "nongranular myelocytes." Weil describes the salient

points of these cells as follows: "They look like a myelocyte whose granules have fused into a smooth homogeneous band of color around the spherical or ovoid nucleus. The protoplasm is homogeneous and deeply stained. . . . In leukemia they are often counted as myelocytes or large lymphocytes by unpracticed observers." Turck has described them under the name "Reizungsformen," and Cabot has found them in the blood of malignant disease and pernicious anemia. We have observed them under similar pathological conditions. The differential diagnosis between the endothelial leukocytes, i. e., the mononuclear transitional type, and the large lymphoblast, is not difficult. The smears do not show the rich violet staining pachychromatic nucleus and the protoplasm gives a distinctly washed out, frosted-glass appearance in contrast to the deeply stained lymphoblast. Peroxidase granules are never present in lymphoblasts while a few are always present in endotheliocytes.

We have found the more satisfactory and uniform method of staining slide preparations to be that devised by Russell; i. e., immersing the slide for one minute in Wilson's or Wright's stain in Coplin jars to fix the film and then three to five minutes in another jar of distilled water containing enough of the stain to tinge the water, usually about five drops. The Hasting's counterstain is omitted.

Goodpasture's stain for differentiating myeloblasts from lymphoblasts is satisfactory and of considerable aid in making the differential count in these preparations. It gives a clear differentiation between the granular and nongranular leukocytes. The differential count is made from a polychrome-methylene blue stain and the Goodpasture stain, allowing for the eosinophils which are undifferentiated by the latter in the total averages.

There still exists considerable confusion regarding the classification of abnormal leukocytes and various hematologists have established a division of their own which in some cases is inclined to be cumbersome. It appears to us not desirable to attempt to subdivide these lymphatic cells. The term lymphoblast is considered preferable to mononuclear leukocyte in describing these cells, as they are nongranular and are apparently of lymphadenoid tissue origin.

Stitt's classification of pathologic leukocytes is considered to be most practical in classifying these cells. He describes this type of cell under the heading of pathologic large lymphocytes as follows: "These are, as a rule, much larger than normal large lymphocytes and show poorer staining of both nucleus and cytoplasm. The nuclei often show the appearance of division into two or more lobes, thus showing the characteristics of Rieder cells. They may be confused with large mononuclears but are considered to be derived from the germinal centers of

various lymphoid tissues. They are found in leukemic and pseudo-leukemic conditions. They never show peroxidase granules. This characteristic, together with sharper outlining of the nucleus, differentiates the pathological lymphocytes (lymphoblasts) from myeloblasts."

These cases all occurred in young adults; each ran a febrile course and each showed enlargement of the lymphatic glands, which, in three of four cases, was quite marked. Enlargement of the spleen was noted in two of the cases. The type of temperature which appears to be characteristic has been commented on already. The frequency of angina is noteworthy in these cases, particularly the presence of the organisms of Vincent's angina noted in three of the cases. However, we had several cases of Vincent's angina in which the blood smears showed no lymphoblasts, so that it is quite evident that this is not the common finding with a Vincent's infection. The possibility that the infection gains entrance through the upper respiratory tract and particularly by way of the tonsils appears to be a reasonable hypothesis. There was no evidence of tuberculosis, lymphosarcoma, or Hodgkin's disease in this series.

The differentiation of this type of case from acute lymphatic leukemia may be particularly difficult. The absence of degenerated and fragile cells in the blood smears, the early return of the temperature to normal, the mild course, the absence of hemorrhagic spots and the absence of particularly high leukocyte counts are distinguishing features. Nevertheless the resemblance to leukemia has been so striking in some of the cases that eminent hematologists have considered it impossible to differentiate this condition on the blood smears alone.

It would appear that the reaction noted in these cases was due to some infectious agent gaining entrance through the upper respiratory passages and resulting in a stimulation of the lymphadenoid tissues with the production of these abnormal cells which, however, disappear in the course of a few weeks or months, leaving the patient in a practically normal condition.

Sprunt and Evans, of Johns Hopkins Hospital, report six cases which resemble our series very closely. They have used the term "infectious mononucleosis" in describing this type of case, and they comment upon the marked similarity of these cases to acute leukemia. All of their cases recovered and all ran a comparatively mild course.

Stitt, in referring to lymphoid pseudoleukemia, states "it is difficult to differentiate this condition from true lymphatic leukemia when aleukemic. The white count varies from 5,000 to 10,000 with about 75 per cent. of lymphocytes. The spleen is enlarged as well as the lymph-nodes and there is a tendency to hemorrhage in the later stages." How-

ever, in our series of cases, there was no tendency to hemorrhage, the leukocyte count in three of the four cases was much higher than 10,000 and the type of cell is distinctly different from that found in lymphoid pseudoleukemia.

The findings in these cases may be summarized as follows:

1. The disease occurred in young adults and as a rule followed an infection of the tonsils or upper respiratory passages.

2. Three of the four cases showed the presence of the organisms of Vincent's angina in throat smears during the acute course of the disease.

3. The blood picture in this type of case bears great similarity to that of acute lymphatic leukemia. However, the total white count never became so large that it could not be accounted for as the result of reaction to acute infection; there was no hemorrhagic tendency and no degenerated or fragile cells were noted in the smears.

4. The predominating type of cell was the lymphoblast and the Rieder type of lymphoblast was frequently noted.

5. All of these cases showed enlargement of the lymphatic glands, particularly the cervical and submaxillary glands.

6. They all pursued a benign course and ended in complete recovery.

7. The term "acute benign lymphoblastosis" is suggested as covering this type of case.

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# FOCAL INFECTION AND SELECTIVE LOCALIZATION OF STREPTOCOCCI IN PYELONEPHRITIS \*

## STUDY I

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In most nonspecific urinary infections, either in the bladder or in the kidney, a gram-negative motile bacillus, believed to be the colon bacillus, is generally the predominating organism in the urine. Naturally, investigation and treatment have been directed against this organism, and patients with pyelonephritis are not considered cured until specimens catheterized from each kidney are found to be free from both bacteria and pus.

Recently, investigators have centered their attention on this organism. During the chill incident to the removal of residual urine in prostatic cases, colon bacilli have been recovered from the blood in as high as 40 per cent. of cases.<sup>1</sup>

Helmholz and Beeler have attempted to produce pyelonephritis experimentally in rabbits by the intravenous injection of colon bacilli obtained from human cases, but only eight of sixty-six animals injected had lesions in the kidney; twenty-one had lesions in other organs.<sup>2</sup> However, during the course of the work, while the urine of the animals was being controlled prior to injection, a rabbit with pyelonephritis was discovered. Cultures from this source injected into thirty-two rabbits produced lesions of the kidney in twenty-five, and in three only were other organs involved.<sup>3</sup>

These findings, together with the work of Brown,<sup>4</sup> Cunningham<sup>5</sup> and others, who obtained the tuberculosis bacillus from the urine of patients with pulmonary tuberculosis but with no complications, and the well known fact that the urine of typhoid patients contains the typhoid bacillus, show clearly that bacteria may penetrate the normal kidney.

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If lesions develop, special conditions, such as the peculiar infecting or localizing power of the bacteria, may be the determining factor. Thus Rosenow<sup>6</sup> has shown that following the intravenous injection of 220 different strains of streptococci, all from sources other than urinary infections, into 883 animals, only 9 per cent. showed lesions in the kidneys, whereas the localization into similar tissue or organs from which the strains were isolated occurred in a far higher percentage of animals. The tendency to localize selectively was so marked in some instances that only the specific organism could be recovered from the lesions even when mixtures of bacteria were injected, a selective action that Forssner<sup>7</sup> has shown can be produced artificially, for he found that bacteria when grown in kidneys or kidney extracts tend to localize in kidney tissue on animal inoculation. This phenomenon possibly explains the selective affinity of the strain of bacteria recovered from the rabbit with pyelitis, illustrating that the specificity might have been acquired and that the colon bacillus may not have been the original infecting agent.

Magoun<sup>8</sup> has shown that bacteria, like certain chemical substances, such as sodium bromid, are capable of being absorbed through the renal pelvis and recovered from the blood stream. Therefore, obtaining positive cultures of the colon bacillus in febrile reactions in urinary infections, although it proves that this bacillus is the cause of the patient's chill, does not prove that the source of the organism was not in the urinary tract. In fact, these febrile reactions occur so commonly following various manipulations in the urinary tract, such as the removal of residual urine, that the occurrence of the colon bacillus in the blood can well be attributed to absorption from the renal pelvis.

Rosenow's work on the elective localization of streptococci has suggested the possibility that oral sepsis, which often occurs in cases of pyelonephritis, may be the focus of infection for bacteria having selective affinity for the urinary tract. Moreover, cases of pyelonephritis have not been considered well treated unless possible oral foci were removed, but that they might be the source of a disease in which the colon bacillus seemed to be the predominating organism is hard to explain because of the low incidence of colon bacilli in oral foci of infection. However, the removal of foci and local treatment of the urinary tract, such as lavage, seemed to be rational therapy. But the

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7. Forssner, G.: Renale Lokalisation nach intravenöse Injektionen mit einer dem Nierengewebe experimentell angepassten Streptokokkenkultur. *Nord. med. Arkiv.* **35**:1, 1902.

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many patients with pyelonephritis who return to clinics year after year for treatment by kidney lavage suggest that the treatment has been directed against the outcome, not against the cause of the disease. We have, therefore, studied a series of patients with pyelonephritis and dental sepsis and we have attempted to ascertain by intravenous injection of the bacteria into animals whether a relationship may not exist between the conditions.

The technic employed in isolating the bacteria and in injecting the animals was that used by Rosenow in similar studies. The material from the infected teeth or tonsils and the urine was spread on the surface of blood-agar plates and inoculated into tall tubes of glucose-brain broth. The cultures were incubated at from 35 to 37 C. The injections, from 3 to 5 c.c., were made intravenously with the primary culture in glucose-brain broth as soon as profuse growth had occurred, usually in from twelve to twenty-four hours. The viability and identity of the organisms injected were determined by plating on blood-agar. The growth thus obtained was then compared with that obtained on the blood-agar inoculated directly. The animals were anesthetized usually from three to six days after inoculation and thoroughly examined for lesions. Cultures were made routinely on blood-agar plates and in glucose-brain broth from the lesions and from the blood, bile, urine, joint fluids, kidneys, and spleen. The character of the lesions was determined by studying sections stained with hematoxylin and eosin, and the causative organism identified in the lesions by gram stain.

As noted in the case histories, the urinary infection was subacute in all of the cases studied.

#### REPORT OF CASES

**CASE 1 (328302).**—Mrs. E. D., aged 30, came to the Clinic, Aug. 6, 1920. The patient's physician wrote that she had suffered for six or seven years with bladder trouble, manifested by frequent and painful micturition, the capacity of the bladder seeming to be limited to about 2 ounces. He suggested that this was the result of extravescical pressure. Eighteen months before he had removed the right ovary and tube, and the appendix, in the hope of relieving the condition of the bladder. The relief was only temporary, and the physician had suggested a hysterectomy. The patient was urinating every five minutes, and intervals greater than one hour were unknown. She dated her trouble from a pregnancy seven years before.

**Physical Examination.**—The physical examination was negative save for a rather marked suprapubic tenderness. The nose and throat failed to show anything suggestive of focal infection. Approximately fifty pus cells to the microscopic field were found in the urine, but many stained specimens failed to show tuberculosis bacilli. A test of kidney function showed a normal return of phenolsulphonephthalein; roentgenograms of the urinary tract were negative. Cystoscopic examination revealed a subacute areal cystitis. Urine obtained from the kidneys showed from one to five pus cells to the microscopic field, and contained colon bacilli. Roentgenograms showed five devitalized teeth and one infected root. Three of the devitalized teeth had definite areas of rarefaction in the apical region; two showed none.

*Comment.*—The cystoscopic findings and the history of the case seemed to indicate a previous rather severe pyelonephritis. The infection had localized in the bladder and apparently was kept up from some source of infection outside the urinary tract. The periapical infection of the teeth was believed to be this possible source. The devitalized teeth, including the two that did not show shadows, were surgically removed and from each pure cultures of green-producing streptococci were isolated.

*Animal Inoculations.*—Six rabbits were injected with the primary cultures in glucose-brain broth and all developed marked lesions in the kidneys (Fig. 1); one also had lesions of the bladder. The streptococcus was recovered from the lesions in the kidney in each rabbit.

Five animals were injected in the second animal passage. Lesions developed in the kidneys of four rabbits, and marked lesions in the bladder in one. One of the rabbits did not show lesions. Again the organism was recovered from lesions in the kidneys and reinjected into three rabbits. Lesions were found in the kidneys of all, but were less marked than those found in the kidneys of the animals in the first and second passages. Of the fourteen



Fig. 1.—Rabbit's kidney with marked swelling and edema of medulla, and areas of hemorrhage and necrosis four days after intravenous injection of streptococci obtained from an infected tooth of the patient in Case 1.

rabbits injected, lesions in the medulla appeared in thirteen, in the cortex in four, and in the bladder in two. Only one of the fourteen was negative. At necropsy the urine of eight contained albumin, pus cells and red blood cells, and seven either pus casts or granular casts. Four had lesions in organs other than the kidney and bladder, but these were relatively slight. Two of the animals had a few pin point hemorrhages in the stomach, another had a few lesions in the muscles, and a third had a small lesion in the myocardium.

*Bacteriologic Investigation.* Cultures were made at necropsy from the kidneys, urine, spleen, bile, liver, blood, and joint fluids, whether or not lesions were present. In all the animals in this series the streptococci were recovered from the kidneys and urine. In ten of the animals all other cultures were negative. Four of the fourteen animals were found dead, and in these four the streptococcus was recovered from the blood, spleen, bile and liver, kidney and urine. In none of the animals did we find colon bacilli in either the kidneys or the urine. A culture made from a catheterized specimen of the

patient's urine early in the investigation showed only gram-negative bacilli. This culture was injected into two rabbits, one intravenously and the other into the bladder. Neither developed lesions of the urinary tract. September 28 the patient had the badly infected root removed. During the severe reaction which followed, the green-producing streptococcus appeared in the urine in large numbers, which still contained gram-negative bacilli. The mixed culture from the urine was injected into two rabbits. Both animals had lesions in the kidneys, and one had a hemorrhagic lesion in the bladder. Cultures from the lesions showed the streptococcus in both animals, and in one a few gram-negative bacilli. Cultures from the urine of both yielded the streptococcus, and of one a few gram-negative bacilli.

CASE 2 (322852).—Mrs. L. S., aged 30, came to the Clinic July 3, 1920, with a history of having had an attack of grippe several months before, and occasional attacks of tonsillitis. She complained of frequent urination and dysuria, a constant pain over the bladder area, which became acute and sharp following urination, and marked loss of weight. At times she was obliged to void three or four times an hour, and stated that an hour and a half was the longest



Fig. 2.—Rabbit's kidney with multiple hemorrhages and small grayish necrotic-like areas in the medulla two days after intravenous injection of streptococci isolated from the lesions in the kidney of an animal previously injected with a suspension of pus expressed from the patient's tonsils in Case 2.

period of retention. The trouble dated from an attack of tonsillitis six years before.

*Physical Examination.*—The physical examination was negative save for some tenderness to deep palpation in the suprapubic region, and evidence of peri-urethral tenderness. A roentgenogram of the urinary tract was negative, and the test of kidney function showed a normal return of phenolsulphonephthalein. Twenty-six pus cells were found in the urine in a single microscopic field. Cystoscopic examination revealed chronic areal cystitis. From one to ten pus cells were found to the microscopic field in urine obtained with ureteral catheters. Colon bacilli were obtained on culture. A test of kidney function by the intravenous injection of phenolsulphonephthalein, with the ureteral catheters in place, showed a return of the dye from each kidney in two minutes; normal amounts were collected at the end of fifteen minutes. A pyelogram of the right kidney showed no evidence of pathologic change due

to infection. The tonsils appeared to have been badly infected previously. One impacted molar was shown in a roentgenogram.

*Comment.*—In this case the urinary infection had evidently persisted in a subacute form, producing but little, if any, damage to the kidneys, as their functional output remained normal and slight infection was demonstrable. The lesions producing the clinical symptoms evidently were the persisting areas of cystitis in the bladder. Because of the pathologic condition found in the tonsils, this also seemed a favorable case to investigate. At tonsillectomy adhesions were found between the capsule and the aponeurosis.

*Animal Inoculation.*—The predominating organisms found in the cultures made from the tonsils were green-producing streptococci and staphylococci. On first animal passage three rabbits were injected, one with a suspension of pus from the tonsils in saline solution, and two with the primary culture in glucose-brain broth. Lesions in the medulla and cortex were found in the

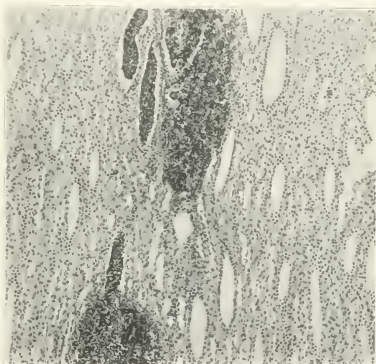


Fig. 3.—Section from rabbit's kidney, showing necrotic area with marked leukocytic infiltration, four days after intravenous injection of culture of streptococci obtained from an infected tooth of patient in Case 1.

three rabbits injected. Only the streptococci were recovered from the infected kidneys; these were reinjected into four other rabbits; two developed lesions in the kidneys (Fig. 2); two did not show lesions. In the third animal passage three rabbits were injected, two intravenously, and one intravesically, with the streptococci isolated from the infected kidneys of the rabbits injected in the second animal passage. There was no evidence of lesions in these rabbits.

Only two of the five rabbits in this series showing definite lesions in the kidneys had sufficient urine in the bladder at necropsy for urinalysis. The urine of both showed a slight trace of albumin and a few red blood cells.

CASE 3 (222711).—Mr. L. M., aged 21, came to the clinic Feb. 21, 1918, with a perirectal abscess that had been discharging for the past two years. Ten months before he had noticed blood in the urine and had experienced

pain at the end of micturition. He had noticed that if he took cold the urinary symptoms were exaggerated. At the time of examination he was obliged to urinate from three to five times at night and from eight to ten times a day.

*Cystoscopic Examination.*—This revealed an easily bleeding, excessively irritable bladder, with a capacity of but 3 ounces, and general diffuse cystitis of a tuberculous type. In passing urethral catheters up to the left ureter multiple obstructions were encountered. In the right side the catheter was passed without difficulty. Specimens from the right side were negative; those obtained from the left showed large amounts of pus. A diagnosis of left pyelonephritis, possibly tuberculous, was made and a nephrectomy performed. The removed kidney showed chronic pyelonephritis. The ureter was as large as a finger, thick walled, and definitely inflamed; the surrounding tissues were markedly edematous. Following this operation the patient's bladder symptoms improved, although they never completely subsided.

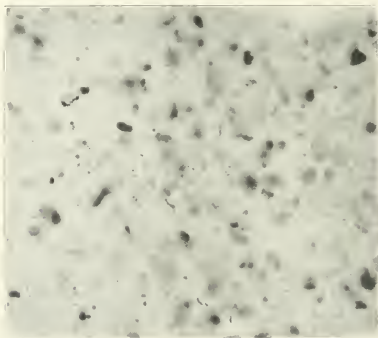


Fig. 4. Diplococci and streptococci in and about leukocytes in the necrotic area shown in Figure 3.

*Subsequent Course.*—When the patient returned to the Clinic, Nov. 25, 1919, his urine still contained a large amount of pus, but repeatedly stained specimens were negative for tubercle bacilli, as were several guinea-pigs into which specimens of the urine were injected. Cystoscopic examination showed a persisting diffuse cystitis; a large amount of pus was obtained from the right kidney, but repeated stainings failed to show any tubercle bacilli. Kidney lavage with mercurochrome and silver nitrate was followed by improvement in the general condition of the patient. Four months later he was discharged, without dysuria, and able to retain his urine for one and one-half hours during the day. He was obliged to get up only twice during the night.

The patient returned to the Clinic a third time, Sept. 22, 1920, with his condition approximately the same. Cystoscopic examination at this time, however, showed but few pus cells in the urine of the right kidney. The teeth

were roentgenographed and the removal of two advised; both were definitely abscessed. The teeth were removed and an acute exacerbation of the urinary symptoms followed. The urine from the right kidney contained much pus and on culture gram-negative bacilli and green-producing streptococci were isolated. Cultures from the infected teeth showed a pure growth of the green-producing streptococcus.

*Animal Inoculation.*—Four rabbits were injected with the primary cultures. All the rabbits showed lesions in the kidneys, and three showed lesions in both kidneys and bladder. In one, in addition to the urinary lesions, a small hemorrhagic area was found in the stomach and in another a slight joint involvement. Three of the four animals had urine in the bladder at necropsy, and in all three red blood cells, pus cells, and a trace of albumin were found. A pure culture of the green-producing streptococcus was obtained from the kidney lesions of all the animals.

CASE 4 (333893).—Mrs. L. H. P., aged 23, was examined at the Clinic, Sept. 14, 1920. She complained of constant pain in the bladder, worse when the bladder was full, and of being compelled to void twelve to fifteen times at night and every twenty to thirty minutes during the day. She had been cystoscoped several times prior to coming to the Clinic. She had an ulcerative cystitis, for which a vaginal cystostomy had been done two years before. This bladder condition had existed for eight years. The patient stated that a short time prior to its onset she had had four teeth devitalized.

*Physical Examination.*—The physical examination was negative. Examination of the nose and throat showed no evidence of a focus of infection. The renal function and blood urea were within normal limits. Urinalysis showed large numbers of pus cells and some red blood cells. A roentgenogram of the urinary tract was negative. Cystoscopic examination revealed a diffuse ulcerative cystitis of very severe grade. Specimens of urine obtained with ureteral catheter showed colon bacilli and a few short chain streptococci. The urine from the bladder contained a similar flora. A roentgenogram of the teeth showed the four devitalized teeth to be definitely abscessed. These teeth were removed surgically and cultures made from two; both yielded large numbers of the green-producing streptococcus. Marked exacerbation of symptoms followed removal of the teeth.

*Animal Inoculation.*—Four rabbits were injected. Lesions were found in the kidneys of three, and slight involvement in the joints of two. At necropsy the three rabbits with lesions in the kidneys had urine in the bladder with pus cells and red blood cells. The streptococcus was isolated from the kidneys of these animals, including the one which did not show gross lesions.

CASE 5 (330369).—Mrs. E. B., aged 47, came to the Clinic, Aug. 19, 1920, for examination because of frequent and painful urination. The patient dated the onset of her trouble from an attack of rheumatism five months before. The attack had been preceded by a severe cold followed by urinary symptoms, which had grown progressively worse. At the time of her examination she was obliged to void hourly day and night.

*Physical Examination.*—The physical examination was negative, including the nose, throat and tonsils. One hundred cubic centimeters of blood contained 20 mg. of blood urea. Roentgenograms of the urinary tract did not show shadows suspicious of stones. A specimen of catheterized urine contained between 50 and 100 pus cells in the microscopic field. Cystoscopic examination revealed a very much irritated bladder with subacute diffuse cystitis. Specimens of urine obtained with ureteral catheters were filled with pus and on culture showed colon bacilli. A normal pelvic outline was shown in a pyelogram of the left kidney, and there was no evidence of structural changes as a result of the infection. An intravenous functional test with the ureteral

catheters in place showed a return of the dye from each kidney in three minutes; normal amounts were recovered fifteen minutes after injection. Roentgenograms showed six devitalized teeth and one root. The root and three of the teeth contained evidence of periapical infection. The remaining three did not show rarefaction.

*Comment.*—This case seemed favorable for study because of the apparent subcuteness of the infection and because the symptoms of the disease had been present only five months. The unimpaired kidney function and the normal kidney outline seemed to argue well for the general improvement of the patient if the source of the infection was removed and the resulting pyelonephritis checked. The infected teeth were removed surgically and an exacerbation of symptoms followed. A pure culture of green-producing streptococci was obtained from each.

*Animal Inoculation.*—Four rabbits were injected with these cultures; one died within the first twenty-four hours, and did not show lesions. Two of the rabbits had lesions in the kidneys, one also had lesions in the bladder. Cultures from the third rabbit were negative. Streptococci were recovered from the lesions in the kidneys and injected into two other rabbits. One had lesions in the kidney, the other, lesions in the bladder. The lesions in the kidneys were in the medulla, similar to those shown in Figures 1 and 2, and those in the bladder were in the mucosa and submucosa. No gross lesions were found outside the urinary tract.

A pure culture of the green-producing streptococcus was obtained from the kidneys and urine of the two animals with lesions of the kidneys. Cultures made from bile, spleen, joint fluid, and blood were negative. In the animal with bladder lesions only, cultures from the kidney were negative, although the urine contained streptococci. Examination of the urine at necropsy showed albumin, pus cells, red blood cells, and granular casts in three rabbits. In the fourth rabbit there was only sufficient urine to culture.

CASE 6 (332441).—Mr. N. R., aged 25, came to the Clinic Sept. 2, 1920, complaining of general malaise, inanition, and insomnia. He had no symptoms of urinary trouble and his general examination was negative.

*Examination.*—Roentgenograms of the teeth showed periapical infection at the roots of four. The tonsils were large and filled with fluid pus. A large amount of pus and an occasional blood cell were found in the urine. Stained specimens were negative for the tuberculosis bacillus. The kidney function was normal as tested by phenolsulphonephthalein. Cystoscopic examination revealed chronic diffuse cystitis with purulent urine. Specimens obtained with ureteral catheters revealed many pus cells in the microscopic field, and on culture colon bacilli were found. The intravenous phenolsulphonephthalein test gave a normal return of the dye in fifteen minutes. It was difficult to determine the duration of the disease because of the lack of urinary history, but as the patient had been in poor general condition for seven months the case seemed favorable for study. The tonsils were removed and cultured and produced countless numbers of green-producing streptococci and many staphylococci.

*Animal Inoculation.*—Two rabbits were injected with emulsion of the extirpated tonsils and two with the cultures in glucose-brain broth. The four animals had lesions of the kidney, two had lesions in the kidney and bladder, three slight lesions in the muscles, and one a small lesion in the myocardium. A pure culture of the green-producing streptococcus was obtained from the lesion in the kidney of each rabbit.

#### SUMMARY

In the foregoing six case histories there is undoubted clinical and cystoscopic evidence of pyelonephritis, accompanied by various degrees



of cystitis. In none of these cases was there any urinary obstruction, either from stone, stricture or prostate, to which the urinary infection might be attributed.

The duration of the disease varied greatly; the longest duration of symptoms, which was eight years, followed the devitalization of four teeth; the shortest duration was five months in a case in which urinary symptoms first occurred following an attack of rheumatism. In one case repeated attacks of grippe and tonsillitis were considered possible etiologic factors, and in three cases the clinical histories gave no suggestion of the source of the infection.

The teeth of the patients had little or no caries; three had a slight degree of pyorrhea. In five of the six cases twenty-one infected teeth, two infected roots, and one impacted tooth were found. Nineteen of the twenty-one infected teeth had been devitalized; in the other two pulp infection followed extensive filling. Sixteen showed periapical infection; five did not show apical rarefaction. Cultures from all but the impacted tooth, which was sterile, produced green-producing streptococci. The primary cultures in glucose-brain broth were injected intravenously into twenty-seven rabbits. Twenty-four (89 per cent.) had lesions in the kidney, and eight lesions in the bladder, four lesions in the muscles, three lesions in the stomach, three lesions in the endocardium, two lesions in the myocardium, and four had joint involvements. The lesions outside the urinary tract were relatively slight in each instance.

#### RESULTS OF ANIMAL INOCULATION

	Strains of Strep-tococci	Animals In-jected	Animals With Lesions in							
			Kid-neys	Blad-der	Kid-neys and Blad-der	Joints	Mus-cles	Stom-ach	Endo-cardium	Myo-cardium
On isolation.....	6	27	24	8	8	4	4	5	3	2
On second ani-mal passage...	3	11	7	2	1	0	1	1	0	1
On third animal passage.....	2	6	3	0	0	0	0	0	0	0

In the second animal passage, the rabbits were injected with streptococci isolated from the kidneys of rabbits that had lesions following injection of the streptococci in the first animal passage. Eleven rabbits were injected with cultures from three strains. Seven rabbits (63 per cent.) had lesions in the kidneys, one rabbit had lesions in the kidneys and bladder, and one had lesions in the bladder. One had slight lesions in the muscles, one in the stomach, and one in the myocardium.

In the third animal passage, six rabbits were injected with cultures

from two strains. Three developed lesions in the kidneys. None of the six showed evidence of lesions in any of the other organs.

The lesions in the kidneys of the rabbits in the first and second animal passages were pronounced (Fig. 3); in the third passage, as affinity for the urinary tract became slighter, the lesions became less marked.

That the marked affinity of these strains for the urinary tract has significance and was not accidental seems certain because during the injection of 208 animals under the same conditions with streptococci from patients having diseases other than urinary infection, only seven developed lesions in the urinary tract. Moreover, experiments in which pus expressed from patients' tonsils was injected without incubation seem to demonstrate that the selective localization of these streptococci was not due to their incubation in artificial mediums or to an overwhelming dosage resulting from their increase in numbers, but to the selective action of the organism isolated. The selective affinity of the streptococci for the urinary tract was so marked that although a mixed culture was injected into some of the animals the streptococcus alone was recovered from the lesions.

Specimens of catheterized urine from all the rabbits were normal before injection; after injection a small amount of albumin with relatively few red blood cells, epithelial cells, and a larger number of leukocytes were usually present.

The kidneys of the animals were usually about normal in size or slightly swollen, and in no instance was the picture that of diffuse parenchymatous nephritis, but always that of localized infection. The capsule stripped readily in all. The cortex often presented small, opaque, yellowish-white areas, and on section the cut surface often revealed marked swelling and edema, especially of the medulla, sometimes associated with areas of hemorrhage varying in size from 1 mm. to 4 mm. Varying numbers of necrotic areas were found in the medulla, some areas so small they were scarcely visible, others large, grayish-white streaks, necrotic-like in appearance, and gradually disappearing as they approached the cortex. These areas were surrounded by zones of congestion and hemorrhage. In only a few instances were hemorrhagic lesions found in the ureters.

On microscopic examination, no evidence of diffuse nephritis was found. The glomeruli were almost wholly free from lesions other than varying degrees of congestion. The necrotic areas showed marked destruction of the epithelium and marked leukocytic infiltration. The parenchymatous cells immediately surrounding these areas were often granular and swollen, and the nuclei of many failed to take the stain. Sections stained by the Gram method showed varying numbers of gram-positive diplococci, singly, in groups, or in short

chains (Fig. 4). The leukocytes often contained many diplococci in various stages of digestion, depending on the duration of the experiments.

#### CONCLUSION

It seems from our study that pyelonephritis may often be due to focal infections harboring streptococci which have a selective affinity for the urinary tract, and that the colon bacillus which is commonly found and generally believed to be the cause, is of secondary importance.

## MUSCULAR INFANTILISM

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Diseases of the nervous system form a somewhat obscure branch of medical science. Our ignorance of the morbid anatomy and histology of many of them is profound. It is, accordingly, a matter of no surprise that our classification of these diseases is unsatisfactory. The intimate correlation between nervous and muscular systems is recognized in the fact that under nervous diseases, every textbook includes descriptions of conditions which are, so far as known, essentially muscular.

There is a tendency to segregate those cases which show muscular atrophy into two clinical groups, the atrophies and the dystrophies. The distinction is probably not well grounded, in respect to etiology. In view, however, of our lack of knowledge of the cause of most of the neuromuscular diseases, even this criticism must be made somewhat tentative. We can recognize the grosser causes of lack of function of the central nervous system, such as cerebral hemorrhage, or an attack of meningitis, but we know very little of the factors which maintain the central nervous system as a going concern; even in the case of the much simpler muscular system there are many unsolved conundrums. Why is creatin always present in muscle? Does it originate in muscle or is it carried from the outside? What mechanism in the muscle transforms it into creatinin, and what is the value of this apparently essential substance in the muscular economy? With the nervous element in the neuromuscular complex remaining shrouded in mystery, there is little cause for wonder that such comparatively common conditions as disseminated sclerosis, progressive muscular atrophy, or pseudohypertrophic paralysis, remain unexplained.

The essence of scientific experiment is to vary one factor at a time, the others remaining constant. In the case of the human subject, it is difficult, almost impossible, to predicate these conditions, but an approximation to them in which there is one outstanding clinical variation from normal and along with it one outstanding chemical variation from normal has come under notice. In the belief that it is a valuable case I venture to place it on record.

### REPORT OF CASE

R. W. T., aged 26, single, bank clerk, consulted me Sept. 25, 1917, because of his inability to perform any unusual exertion, or, in fact, anything more than a comparatively small muscular effort would accomplish. There was no history of tiring easily; provided, the muscular work called for was small in

intensity, the effort could be maintained as long as it could be by the ordinary person, but when the effort called for was more than a very small amount, it simply could not be performed. Thus he could walk about all day, and perform to the full his duties as a bank clerk; he could enjoy a game of golf, but

TABLE 1.—PATIENT'S FAMILY HISTORY ON FATHER'S SIDE

		1. Female, affected, still living, 75, six in family	1. Male affected { 1. Male, free } 2. Male, free 2. Male, affected, no family 3. Female, free, no family 4. Male, free, two children, both free 5. Male, affected, unmarried 6. Female, affected, no family
		2. Female, affected, still living, 73	{ 1. Male, free, do not know about family 2. Male, affected, unmarried 3. Female, free, two children
		3. Female, free, died at 36 years, inflammation of bowels	{ 1. Male, free, no family 2. Male, free, no family 3. Male, affected, unmarried
		4. Male, free, still living; seven children, all free	
		5. Female, free, died at 18, summer complaint	
		6. Male, affected, still living	{ 1. Male, free, 1 male, free I think 2. Female, free, no family
	1. Female, affected, "Dad's" mother	7. Male, affected, (father of R.W.T.), still living	{ 1. Male, free } 1. Male, free 2. Female, free 3. Female, affected, unmarried 3. Male, affected, unmarried 4. Male, free, unmarried 5. Male, affected, (R.W.T.) 6. Female, free
		8. Male, affected, died at 45, Bright's disease	{ 1. Male, five children, all free 2. Female, free 3. Male, affected 4. Female, free, three children, don't know about them 5. Male, affected 6. Female, free, no family 7. Female, free, unmarried 8. Female, free, unmarried
	"Dad's" grandmother, affected	9. Female, affected, died at 53, cancer	{ 1. Female, free, unmarried 2. Male, free 3. Female, affected, unmarried
		10. Female, died at 3	
		11. Female, free, died at 27, consumption	{ 1. Male, free, unmarried 2. Female, free, died
		1. Female, free, died, don't know about family	
		2. Male, affected, no family	
		3. Male, free, family free	
	2. Female, affected, "Dad's" aunt	4. Male, free, don't know about family	
		5. Female, affected	{ 1. Male, free 1. Female, affected { 1. Male, free 2. Male, free 2. Male, free
		6. Female, free, family all free I think	
		7. Male, affected	{ 1. Male, affected 2. Female, free
	3. Female, free	8. Male, family free so far as I know	

throwing a baseball or rowing a boat were sheer impossibilities, while even such ordinary activities as taking a high step or rising from a sitting to the upright position without the assistance of his hands, were difficult. He had been aware of this condition since he was a child. His health has always been good, and within limits his enjoyment of physical activity has always been

as great as that of his neighbors. The physical limitation has never been associated with mental weakness or psychic change of any sort, apart from the recognition that his muscular weakness handicapped him in juvenile sports. He knows that his father, and his father's mother have the same weakness.

*Family History.*—It was possible to obtain a fairly complete family history, dating back to the patient's paternal great grandmother, and passing down through his paternal grandmother and his father to himself. From a study of Table 1 it will be seen that the condition affects both male and female, that with one exception—if the observation be correct—those who are themselves free from the condition, whether male or female, do not transmit it to their children. That exception is the third oldest of "Dad's" sisters, who while free herself had a son who is affected. This individual, my patient states, is much the worst of all, being "pretty helpless." It further shows that the condition is not one which predisposes to any particular disease, does not of itself shorten life, and in no way interferes with the reproductive powers. Analysis of Table 1 shows further that of twenty-six males liable to be affected, fourteen were so affected, and twelve were free. Of twenty-one females, seven were affected while fourteen were free.

TABLE 2.—PHYSICAL MEASUREMENTS OF PATIENT

	Left, Inches	Right, Inches	Inches
Biceps.....	9 $\frac{5}{8}$	10	
Forearm.....	8 $\frac{3}{4}$	9 $\frac{1}{4}$	
Wrist.....	5 $\frac{1}{2}$	5 $\frac{1}{2}$	
Thigh.....	21 $\frac{1}{4}$	22	
Leg.....	13	13	
Knee.....	13 $\frac{1}{4}$	13 $\frac{1}{4}$	
Calf.....	14	14	
Ankle.....	8 $\frac{3}{4}$	8 $\frac{3}{4}$	
Chest.....			38
Waist.....			32 $\frac{1}{2}$
Abdomen and hips, at most prominent circumference.....			38 $\frac{3}{4}$

*Physical Examination.*—Examination shows apparently little departure from the normal. The patient is 5 feet 8 inches tall and weighs 155 pounds. He is distinctly adipose, the fat being largely distributed in the general subcutaneous tissue, so that there are rounded outlines suggestive of the female rather than the male figure. This suggestion is accentuated by the presence of striae over the lower abdomen and upper part of the thighs, some of these being white and glistening, others purplish, exactly like typical "striae gravidarum." He has no recollection when these appeared. He underwent no sudden or even rapid increase in bulk, and is not now thinner than he has been, so that the explanation of the striae is somewhat obscure. This relative adiposity is, the patient states, not characteristic of the condition. He is himself, he says, the only one he knows of who shows it. The majority of those affected are normal in outline, all, however, being characterized by the presence of small bones. The probability is that the smallness of the bones is directly correlated with the limited power of the muscles. The wrist measurement, for example, in this case is about 5 $\frac{1}{2}$  inches. The average female wrist is about 6 inches, and the average male wrist is about 6 $\frac{3}{4}$  inches.

Two other characteristics of those affected are the presence of distinctly square shoulders and a short neck.<sup>1</sup>

1. A fairly complete examination has been made from time to time, and in this respect I am indebted to Professor Swale Vincent, of the Department of Physiology, University of Manitoba, now of the University of London, to Professor William Boyd of the Department of Pathology, University of Manitoba, and to Dr. Robert G. Armour of Toronto, for observation along special lines.

Examination of the circulatory, respiratory and alimentary systems revealed no abnormality. The blood pressure (systolic) has varied from 130 to 140. The urine has shown no albumin, blood, sugar or pus. The thyroid is very slightly enlarged.

*Blood Examination.*—Investigation of the blood was done from time to time. The red cell count has always been above normal, varying from 6,230,000 to 5,760,000. The leukocyte count has always been about normal, the highest observation being 12,400, the lowest 7,600. The hemoglobin is also within the limits of normal variation, from 75 to 90 per cent. being the limits. This, it will be observed, gives a rather lower color index than normal.

The differential leukocyte count has followed at all times strictly normal lines, averaging: polymorphonuclears, 75 per cent.; small lymphocytes, 20 per cent.; large lymphocytes, 3 per cent.; eosinophils, 2 per cent.

*Roentgen-Ray Examination.*—Roentgenograms were taken of the skull with a view to determining whether or not there was any increase in the size of the pituitary fossa. No variation from normal has been observed.

*Examination of the Central Nervous System.*—This examination was made at my request by Dr. Robert G. Armour of Toronto. His report is as follows:

Feb. 5, 1919: Shoulders broad and high; pelvis narrow; musculature of thighs apparently good, tapering markedly from hips to knees; calves well developed; musculature of arms poor, about size of those of boy of 16; no obvious wasting of any particular muscle or group; fingers moderately small and tapering, not deformed; toes slightly "hammer"; in standing, appear to spread. He has always had trouble in getting boots to fit him on account of the width of the feet at the base of the toes. Marked callosities under transverse arch of feet. Station, with eyes closed, good. On either leg alone and eyes closed, fair. On left not quite so steady as on right. Tends to trip or slip easily. Gets up from a lying position fairly readily, with no attempt to "climb up" himself. Can walk on toes, but has difficulty in rising on heels. No appearance of atrophy of peroneal muscles. Moderately good strength of leg muscles, although below average, and low in proportion to appearance of development. Strength of biceps and triceps of arms inconsiderable.

Grasp of hands each 16 on dynamometer (average normally 45). No inequality in strength of facial muscles of two sides. Retraction of mouth not well performed, and extreme efforts cause little wrinkling of the face. No apparent weakness of upper face. Mouth opened and tongue protruded, and palate elevated to full extent and in middle line. No ptosis. Eye movements full in all directions. No nystagmus. Pupils react briskly to light and accommodation. Fundi normal. Moderate pes cavus.

Reflexes: Knee jerk present, easily elicited, not increased, no clonus. Idiomyuscular contractility not obtained over quadriceps extensor. Ankle jerk easily elicited, no clonus, equal, idiomyuscular contractility obtained in calf muscles. Attempts to elicit this in extensors and peroneals cause contraction of the calf muscles which raise the heel from the ground. When this is prevented, no idiomyuscular contractility is obtained. Biceps and triceps reflexes of upper extremity easily elicited. Idiomyuscular contractility present in triceps, extensors of forearms and doubtful in deltoids. Not present in biceps, pectorals or trapezii. Present to a slight degree in the facial muscles. Plantar, plantar flexion, but feeble. Cremasteric reflex doubtful. Abdominal and epigastric reflex doubtful.

No sensory change demonstrable, including position sense. No tachycardia. All muscles react to faradism.

*Examination of the Eyes.*—This examination was made for me by Dr. Harvey Smith. His report is: "I find that he has a small error of refraction. Fundus examination is negative, nor can I discover any defect in his field or in his pupillary reflexes."

The Wassermann reaction was negative. There was slight enlargement of the thyroid gland.

*Treatment.*—At the suggestion of Professor Swale Vincent, raw suprarenal glands were administered. One ox gland per day was taken, minced, as a sand-

wich, commencing Nov. 1, 1917. This was continued until Dec. 18, 1917, when because of some nausea this feeding was stopped. Ergographic tracings made before and after the administration of suprarenal gland seemed to indicate slight improvement in the muscular condition, but it was not striking.

Jan. 25, 1918, suprarenal gland feeding was resumed at the rate of one-half ox gland per day. This was continued until March 14, 1918. No appreciable increase of muscular power was noted, although there was some gastric instability. The taking of suprarenal gland was, therefore, definitely stopped.

May 17, 1918, a course of graduated exercises was commenced. These were of a simple nature designed with a view to increasing the existing muscular development. They were continued until June 26, 1918, when there was added to the exercises a course with the Bristow coil, an instrument which in other cases has proved of considerable value in increasing the bulk of atrophied muscles.

Oct. 15, 1918, his measurements were again taken.

TABLE 3.—PHYSICAL MEASUREMENTS ELEVEN MONTHS AFTER TREATMENT WAS BEGUN

	Left, Inches	Right, Inches	Inches
Biceps.....	10	10 $\frac{1}{8}$	
Forearm.....	9 $\frac{1}{8}$	9 $\frac{1}{8}$	
Wrist.....	5 $\frac{1}{2}$	5 $\frac{1}{2}$	
Thigh.....	21 $\frac{1}{2}$	22	
Leg.....	13 $\frac{3}{8}$	13 $\frac{3}{8}$	
Knee.....	13 $\frac{1}{2}$	13 $\frac{1}{2}$	
Calf.....	14	14 $\frac{1}{2}$	
Ankle.....	7 $\frac{3}{8}$	7 $\frac{3}{8}$	
Chest.....			38
Waist.....			33
Abdomen and hips.....			39 $\frac{1}{2}$

These measurements are confirmatory of the opinion expressed by him that his muscular power was little, if any, increased.

*Subsequent Course.*—In the spring of 1919, the patient had an attack of influenza and was ill for three weeks. The summer he spent at work in the country and I did not see him again until Sept. 22, 1919. The measurements then were as follows:

TABLE 4.—PHYSICAL MEASUREMENTS ELEVEN MONTHS AFTER CESSATION OF TREATMENT

	Left, Inches	Right, Inches	Inches
Biceps.....	10	9 $\frac{3}{4}$	
Forearm.....	8 $\frac{7}{8}$	8 $\frac{5}{8}$	
Wrist.....	5 $\frac{5}{8}$	5 $\frac{5}{8}$	
Thigh.....	21 $\frac{1}{2}$	21 $\frac{3}{8}$	
Leg.....	13	13 $\frac{1}{4}$	
Knee.....	13 $\frac{1}{2}$	13 $\frac{1}{4}$	
Calf.....	14	14 $\frac{1}{2}$	
Ankle.....	7 $\frac{3}{8}$	7 $\frac{3}{8}$	
Chest.....			39
Waist.....			33
Abdomen and hips.....			38

These show practically no alteration from those previously noted. In other words, he seemed to be as well without treatment of any sort as with it.

The muscles themselves, though not at all massive, are not abnormally small for a man of his build. The electrical reactions were tested and gave a response of normal quality to both faradism and galvanism. A small piece of muscle was excised from the right vastus lateralis muscle and sent for histologic



examination to Professor William Boyd. His report indicates practically no departure from the normal.

*Microscopic Examination.*—Portions of the vastus lateralis muscle, removed under local anesthesia, were examined by the usual methods. The only marked deviation from the normal was the wide separation of the muscle fibers from one another by what appeared to be edematous fluid. This, however, was probably merely the result of the injection of novocain. The individual muscle fibers appeared to be slightly atrophic, but the transverse striations were quite distinct, although, perhaps, not quite so prominent as in the normal fibers. The nuclei of the sarcolemma were well developed. There was no evidence of any of the increase of fat which is so characteristic a feature of the pseudohypertrophic form of muscular dystrophy.

From April 20, 1920, until June 6, 1920, thyroid gland was given, 15 grains per day. During treatment with thyroid gland he had an excess of carbohydrate. The result of this was certainly not an improvement clinically, and examination of the urine suggests that the results were bad. Pituitary extract, 15 grains per day was taken from June 14, 1920, until July 7, 1920. Again no improvement was shown. Strychnin,  $\frac{3}{55}$  grain, was also used from Sept. 13, 1920, until Sept. 20, 1920, with equally unfavorable consequences.

From time to time the patient has been examined by Prof. Swale Vincent and by Prof. A. T. Cameron. Professor Vincent's report is as follows:

March, 1920: The patient has a fairly good power of long sustained effort of a low grade. He walks fairly well and can play eighteen holes of golf without much fatigue. He can raise a 25 pound bar above his head four or five times. He can hang onto a horizontal bar for a moment, but cannot raise himself in the least. There has been some increase in the strength of his arms since 1917.

The dynamometer record has also slightly improved since 1917. The results have varied between 40 and 50 kilograms tested by Verdin's (Boulitte's) dynamometer. Mosso's ergograph has not given very accurate results because of the long time during which the patient could continue minimal contractions. With the right second finger the laboratory attendant could execute 400 kilogram centimeters of work when each complete movement was carried out in two seconds. The patient could only raise the weight five or six times, doing at most from 12 to 15 kilogram centimeters of work. Roughly, then, his muscular power is about 4 or 5 per cent. of the normal.

#### CHEMICAL REPORT

The observations have been carried out between March and October, 1920. As during this period the patient was carrying out his usual duties, it was impossible to conduct an exact supervision of diet. As soon as the creatinuria was definitely associated with his condition, further observations were directed chiefly to the effect of treatment on this symptom. As the degree of creatinuria did not appear to be materially affected by a moderate meat diet, no special diet conditions were imposed, but full particulars were obtained of the nature of the meals on the days on which twenty-four hour urine samples were obtained.

*Urine Examination.*—The following methods were employed: The total phosphates were estimated by the uranium acetate method. Chlorids were estimated by the Volhard-Arnold method. Uric acid was determined by the Benedict-Hitchcock modification of the Folin-Macallum-Denis procedure. Acidity and total ammonia and amino-acids were estimated by the formal titration method. Creatin and creatinin were determined by the Folin-Benedict method, using a Kober colorimeter. The creatin figures are expressed in terms of creatinin. Urea was approximately determined by the Hinds-Doremus ureometer.

Nothing specially abnormal was observed in the color, appearance or specific gravity. Indican was only present in normal amounts. The acetone bodies (tested for by Le Nobel's, Gerhardt's, Hurtley's, and Rothera's reactions) were almost invariably absent. The exceptions are noted. Reducing sugar and albumin were invariably absent. Urinary sediments were not abnormal.

The figures in Table 5 refer to grams in the twenty-four hour sample, except those for acidity, expressed in cubic centimeters of tenth normal alkali.

May 9, an extremely hot day, more water than usual was drunk, less urine than usual was excreted, and the Le Nobel and Gerhardt tests for aceto-acetic acid, and the Rothera test for acetone were distinctly positive. June 11, the Rothera test was positive, the Le Nobel test just positive, and the Gerhardt test negative.

TABLE 5.—RESULTS OF EXAMINATION OF URINE

Date	Total Volume in C.c	Acidity	Ammonia and Amino-Acids	Urea	Uric Acid	Phosphates	Chlorides	Creatinin	Creatinin plus Creatin	Creatin	Diet
3 2	1,050	252	0.43	22	0.43	2.56	.....	1.09	1.47	0.38	Normal; some roast beef
3/ 9	2,250	445	0.82	27	0.51	2.41	9.27	0.81	1.72	0.91	Meatless on March 8 and 9
3 31	1,725	642	1.12	17	.....	.....	16.58	0.90	1.31	0.41	Normal; meat with two meals
4/16	1,785	512	0.94	32	.....	2.4	.....	1.45	1.80	0.35	Normal; some fish
4 17	1,345	439	0.92	30	.....	2.1	.....	1.26	1.84	0.58	Meat with two meals
4/18	2,040	414	0.81	28	.....	1.9	.....	1.22	1.71	0.49	Somewhat less meat
4 27	1,445	.....	.....	..	.....	2.05	.....	0.90	1.52	0.62	Meatless, thyroid from April 20; with excess sugar
5 7	1,575	431	0.63	28	.....	.....	.....	0.85	1.70	0.85	Some fish; thyroid; sugar
5 8	1,250	393	0.75	21	.....	.....	.....	0.90	1.30	0.40	Meatless; thyroid; sugar
5 9	790	458	0.78	21	.....	..	.....	0.85	1.42	0.57	Some meat; thyroid; sugar
6/ 4	1,300	1830	1.80	21	.....	2.4	.....	1.14	1.24	0.10	Meatless; thyroid; sugar
6/ 5	1,350	945	2.12	22	.....	2.4	.....	1.12	1.28	0.16	Meatless; thyroid; sugar
6/ 6	1,240	840	1.42	22	.....	2.4	.....	0.95	1.24	0.29	Chicken; thyroid; sugar
6/11	1,440	499	1.04	30	0.78	.....	.....	1.48	2.20	0.72	Fish and meat; thyroid stopped since June 6; excess of sugar continued
6/29	1,300	343	0.58	21	.....	.....	.....	1.09	1.52	0.43	Some meat; pituitary and excess sugar since June 23
6/30	1,470	448	0.81	21	.....	.....	.....	1.04	0.50	0.53	As previous day
7/ 1	1,750	266	0.62	18	.....	.....	.....	0.81	1.16	0.35	As previous day
8/27	1,050	.....	.....	..	.....	.....	.....	1.33	1.89	0.56	No treatment; some fish
8/28	1,320	.....	.....	..	.....	.....	.....	1.33	1.85	0.52	As previous day
8/29	1,145	.....	.....	..	.....	..	.....	0.94	1.25	0.31	Meatless
9 19	1,095	245	0.60	..	.....	.....	.....	0.89	1.37	0.48	Some meat; strychnin since September 13
9/30	1,870	274	0.75	..	.....	.....	.....	0.82	1.27	0.45	As previous day
9 21	1,760	289	0.62	..	.....	.....	.....	0.86	1.21	0.35	As previous day, but strychnin stopped September 20

While the urea figures are distinctly low, the only distinct abnormality is the continual presence of creatin. The creatinin excretion for a man of about 68 kg. with some body fat should be about 1.4 gm. per day. The figure in Table 5 is almost always less, and is only three-fourths of this on a meatless diet. There is some indication that the excretion of creatin tends to diminish slightly on a meatless diet, though the results for meatless days include the highest figure recorded. The creatin figures are consistently high, varying between 40 and 110 per cent. of the creatinin figures.

Administration of thyroid with excess cane sugar caused for several weeks an increase in the amount of creatin, in agreement with the observation of Cramer and Krause that thyroid medication causes creatinuria, and the occurrence of creatinuria in exophthalmic goiter. Continued administration of thyroid over a prolonged period, while apparently increasing the creatinin toward

a normal figure, and giving the lowest degree of creatinuria recorded, produced marked acidity, with a concomitant feeling of the patient that he was not so fit, and a distinct decrease of muscular strength, as indicated by the ergograph, so that the initial rise of creatin can be regarded as indicating an adverse effect. The cause of the marked hyperacidity was not ascertained. It was not due to increase of phosphates, nor to acetone bodies nor to lactic acid.

Pituitary produced no effect. Strychnin appeared to decrease the creatinin without producing any effect on the creatin. This effect can, perhaps, be regarded as nonbeneficial, in line with the general effect on the patient and the ergographic record.

In order to study the creatinuria more closely, the urine was collected at three hour intervals on Sunday, September 5. A final collection was made for the nine hour period ending at 8 a. m. September 6. In this, as in previous work, the patient's accuracy had to be relied on. The total amount passed was very low, but assurance was given that the amount was collected accurately. The diet was meatless, otherwise normal, and the patient had been undergoing no special treatment for the previous two months. The results are shown in Table 6.

TABLE 6.—RESULTS OF STUDY OF URINE WITH PATIENT ON A MEATLESS DIET AND UNDER NO SPECIAL TREATMENT

Time	Volume, C.c.	Acidity, C.c.	Ammonia Plus Amino-Acids, Gm.	Creatinin, Gm.	Creatin, Gm.	Acidity per 100 C.c.	Ammonia Plus Amino-Acids, Gm. per 100 C.c.	Creatinin, Gm. per 100 C.c.	Creatin, Gm. per 100 C.c.
11 a. m.	180	41	0.031	0.15	0.09	23	0.073	0.08	0.05
2 p. m.	100	35	0.077	0.11	0.04	41	0.077	0.11	0.04
5 p. m.	85	31	0.069	0.12	0.05	37	0.081	0.14	0.05
8 p. m.	72	34	0.069	0.08	0.05	47	0.096	0.11	0.07
11 p. m.	44	31	0.053	0.06	0.03	71	0.121	0.14	0.07
8 a. m.	215	150	0.294	0.27	0.12	70	0.137	0.13	0.06
Total	696	322	0.69	0.79	0.37				

These results, especially when expressed per 100 c.c. of urine, indicate that the creatin concentration in the urine is approximately constant throughout the twenty-four hours, but tends to increase slightly with increased acidity and ammonia. The creatinin figures do not show this relationship. This constant excretion of urine throughout the twenty-four hours is not in accordance with other observations on cases of creatinuria. It will be discussed further elsewhere.

*Blood Sugar.*—Blood sugar was estimated April 2. A sample was taken in the morning, before breakfast. One-tenth per cent. glucose was present (Benedict's modification of the Lewis and Benedict method). A breakfast was given consisting of 200 c.c. of milk, 100 gm. bread and butter, and 100 gm. glucose. After two hours the blood sugar was 0.15 per cent. The urine contained no reducing sugar throughout the day, and the feces contained none on this nor on the two succeeding days.

*Sugar Tolerance.*—April 11, two hours after a moderate breakfast, a similar sugar meal was given, with cane sugar substituted for glucose. No reducing sugar was detectable in the urine throughout the day. The carbohydrate metabolism was, therefore, apparently normal.

*Blood Creatinin and Creatin.*—A sample of blood was obtained Nov. 28, 1920, two hours after breakfast. The creatinin estimated by Folin's method, amounted to 0.7 mg. per 100 c.c. blood. This is the minimal figure for normality. The creatin was not determined, since according to Hunter and Camp-

bell<sup>2</sup> and Feigl<sup>3</sup> the present methods do not yield results sufficiently accurate to warrant any conclusions being drawn. A sample of urine obtained at the same time showed, per 100 c.c., 113 mg. creatinin and 46 mg. creatin.

It may be noted that the blood appears to clot somewhat more readily than normal.

*Comment.*—Most of the interest of Professor Cameron's report centers around the presence of creatinuria. In considering the results of examination, one must bear in mind the fact that during the whole time of observation the patient has been engaged in his ordinary work. Modifications of diet were for the most part carried out without control. The patient has lent himself to investigation in the most willing and intelligent manner.

The chemical findings may be summarized as follows:

1. The creatinin excretion suggests the actual extent of musculature which he possesses.
2. The creatin excretion suggests an infantile condition.
3. The creatin + creatinin excretion is in agreement with the musculature of a normal individual of his build.
4. The creatin excretion varies little on meat diet.
5. The blood sugar is normal.
6. Sugar utilization is normal.
7. Acetone bodies were present on one occasion only. The creatin for this day was not a maximum. Acetone bodies have no special relation to this condition.

Regarding the influence of treatment it may be said that:

1. During suprarenal administration no chemical examination was made, Professor Cameron being still on active service.
2. During thyroid administration excessive carbohydrate was used without obviously modifying the thyroid effect. (a) There was initially a slight increase in creatin which lasted two or three weeks. (b) After six weeks there was a marked fall in creatin and no appreciable change in creatinin. (c) There was marked acidity of the urine, cause undetermined.
3. Pituitary had no effect. This was noted in spite of carbohydrate being still used in excess.
4. Strychnin apparently decreased creatinin without any marked effect on creatin. This was accompanied by unfavorable ergographic records. Subjectively, the physical condition was also less satisfactory. (Other factors may have entered here to contribute to this.)

Result of a twenty-four hour test on meatless diet was:

1. Creatin was excreted constantly.
2. There was no particular relation to creatinin.

2. J. Biol. Chem. **33**:169, 1918.

3. Biochem. Ztschr. **105**:255, 1920.

3. There was increase of creatin with increase of ammonia and acidity.

4. Creatin excretion did not fall off during the night.

5. The kidneys removed creatin from the blood at a fairly constant rate per c.c. of urine.

A word or two is necessary regarding the ergographic tracings. The earlier ones are comparatively valueless on account of the fact

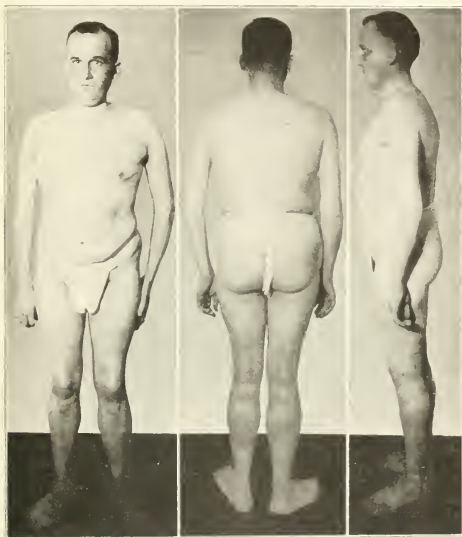


Fig. 1.—Three views of patient showing amount and deposition of fat.

that a small load was used; the patient was able to raise this almost indefinitely; in other words, for a small load his endurance was considerable. In this respect the tracing is infantile in character.

In the later tracings a load of 2,000 gm. was used and in most cases the observation was controlled by a corresponding observation on the laboratory attendant. In every case, the load was 2,000 gm. and each complete movement was carried out in two seconds.

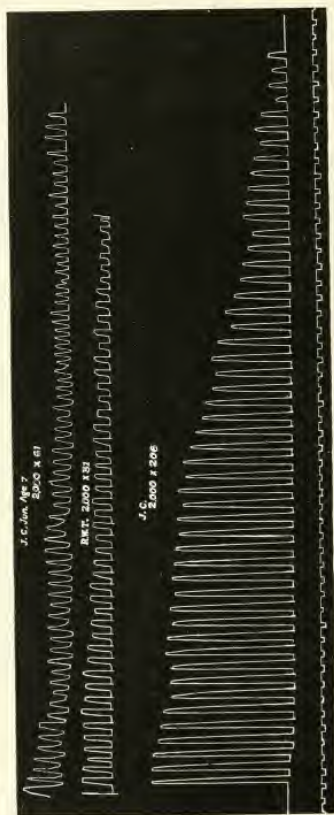


Fig. 2.—Ergographic tracing.

Table 7 shows a tracing of R.W.T., J.C., (the laboratory attendant), and J.C., Jr., the son of the latter, aged 7 years 2 months. With a load of 2,000, the child has an excursion of 61, as against R.W.T.'s average which is well under 40. This child was still normally excreting creatin.

The observation on May 9, 1920, corresponds to a time when he had been taking thyroid, 15 grains, per day for about twenty-one days. The tracing of June 6 was taken on the last day of thyroid administration and showed a drop to 10, the lowest recorded in the series. The dynamometer record on this day was 40, so that the loss was in endurance rather than in power. On all grounds, therefore, the taking of thyroid produced undesirable results.

TABLE 7.—ERGOGRAPHIC TRACINGS OF PATIENT AND TWO NORMAL SUBJECTS

Date	Name	Excursion	Dynamometer
5/ 9/20.....	R. W. T.	26	
	J. C.	206	
6/ 6/20.....	R. W. T.	10	40
	J. C.	249	
6 12/20.....	R. W. T.	21	38
	J. C.	236	
7 2/20.....	R. W. T.	26	39
	J. C.	220	
9/12/20.....	R. W. T.	39	40
	J. C.	230	
9/21 20.....	R. W. T.	26	39
10/24 20.....	J. C., Jr.	61	

June 12, six days after ceasing to take thyroid, a rise to 21 had occurred.

June 14, the administration of pituitary was commenced, and a tracing taken July 2 showed the figure 36, practically a return to the normal for him.

Before commencing strychnin administration September 13, a tracing was taken September 12. The patient was feeling exceptionally well, and this was reflected in the number 39.

Strychnin was stopped September 20, and the following day the observation showed a drop to 26. Throughout the whole experiment, the dynamometer record has varied very little; the ergographic tracings have given much more valuable information, revealing variations in total work capacity rather than in degree of effort.

In considering the diagnosis of this condition, one is at once met with the striking absence of pathologic signs, except the infantile degree and character of muscular power; and the presence of creatin in the urine.

On clinical grounds, the varieties of progressive muscular atrophy are inadmissible, inasmuch as the condition is not progressive, nor is there evidence of muscular atrophy. Myasthenia gravis, amyotonia

congenita and pseudohypertrophic paralysis are mentioned merely to be dismissed.

What, then, is the condition? Is it a pathologic entity resulting from disease of or lack of development of some part of the nervous system, or some of the endocrine glands, or is it some inherent variation in muscle tissue? No support is given to the latter theory by histologic examination of muscle tissue. The solution of the mystery is closely bound up with the metabolism of creatin, regarding which many scattered pieces of evidence of variable trustworthiness are available, but regarding which no satisfactory evidence has been adduced of the source of supply or the mechanism of its transformation into creatinin. Creatin is normally present in young children and abnormally present in some pathological states. Why it should disappear as maturity is reached we do not know.

On the basis of clinical data, of ergograph and dynamometer records, and the presence of creatin in the urine, I venture to describe this as a case of muscular infantilism. Its ultimate cause is still unknown, and the condition is entirely uninfluenced as yet by treatment. Such observations as have been made tend to negative the suggestion that the endocrine glands are at fault.



## ADMINISTRATION OF A PITUITARY EXTRACT AND HISTAMIN IN A CASE OF DIABETES INSIPIDUS \*

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We have recently had the opportunity to study experimentally a rather severe case of diabetes insipidus. Our observations include the effect of lumbar puncture, the administration of pituitary extract hypodermically and by mouth, the effect of histamin injection, the nitrogenous metabolism before and as affected by pituitary extract, the blood constituents and the carbohydrate tolerance.

### REPORT OF CASE

J. S., male, white, aged 24 years, single, a painter and mechanic, and an overseas man, was referred to the State University of Iowa Hospital, April 25, by Dr. F. H. Lamb of Davenport, Iowa, for chronic syphilis and polyuria.

*Family History.*—The family history was unimportant; the patient stated, however, that one brother is a great water drinker.

*Present Illness.*—The patient complained of loss of appetite, pain in the back and lower abdomen, occasional dimness of vision, dizziness, coldness and chills, polydipsia and polyuria, general weakness, and some loss in body weight (from 145 to 133 pounds). The syphilitic history dates from an exposure Sept. 15, 1915; sores developed on the penis and then in the throat in October following. He received some treatment at this time. In 1916, he had gonorrhea. In February, 1920, he was found to have a + + + + Wassermann reaction, and received some syphilitic treatment. A test made just before he entered this hospital was still + + + +, and another test after admission was + + +. It was difficult to get a statement as to the existence of a polyuria previous to the syphilitic infection, though that such may have obtained and become intensified subsequently is not excluded. The patient's trials in getting water to drink while a soldier in the front lines were particularly distressing.

*Physical Examination.*—Little of importance was found. There was no evidence of hypopituitary or hyperpituitary change.

*Laboratory Examination.*—The urine was free from protein and sugar. The blood gave 93 per cent. hemoglobin; 4,260,000 red cells and 7,200 leukocytes, with polymorphonuclears 72 per cent., lymphocytes 26 per cent., and eosinophils 2 per cent. Systolic blood pressure was 104 mm., diastolic 62 mm., and pulse pressure 42 mm.

The cerebrospinal fluid obtained May 1 by lumbar puncture was under no increased pressure; about 5 c.c. of clear fluid were drained. The Wassermann test was negative, Noguchi + +, and the fluid contained no cells.

The roentgenogram of the cranium shows a somewhat enlarged sella turcica with processes sharply defined. It is not to be regarded as abnormal.

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In Table I is given a summary of the twenty-four hour observations on the output and concentration of the urine during the period the patient was in the metabolism ward. On the first, sixth and seventh days, the nitrogen distribution in the urine was also determined. With the exception of the first day, the urine was collected hourly during the day, but the night urine (from 7 p. m. to 7 a. m. or from 8 p. m. to 8 a. m.) was mixed and measured in toto. Minimal and maximal specific gravities are therefore given. The nitrogen intake is calculated from the protein of the diet. The salt intake does not include the chlorid of the raw food, and, accordingly, a negative salt balance is shown. No salt was used in the preparation of the diet, but the patient was permitted salt ad libitum from a weighed container. The diet was essentially purin free and creatin free.

TABLE 1.—SUMMARY FOR TWENTY-FOUR-HOUR PERIODS

Day	Water Intake	Urine		Food N	Urine N		NaCl Intake	Urine NaCl		
		Volume	Sp. Gr.		Gm.	Per Cent.		Gm.	Per Cent.	
1	16,820	15,200	1.002	11.68	11.25	0.074	3.45	7.00	0.046	
2	15,370	16,800	1.001	12.16	9.95	0.060	4.78	6.76	0.040	
3	17,380	18,605	1.002	12.80	10.15	0.054	5.70	10.87	0.058	Lumbar puncture
4	25,000	19,075	1.002	12.64	9.02	0.047	8.21	8.83	0.046	
5	8,590	5,110	1.001	12.48	8.16	0.159	5.38	9.22	0.180	Pituitary extract hypodermically
6	4,120	4,190	1.014	17.12	7.74	0.185	14.81	3.25	0.077	Pituitary extract hypodermically
7	8,860	10,615	1.001	12.96	8.77	0.082	4.11	13.57	0.129	
8	9,660	11,975	1.001	13.12	9.46	0.079	11.61*	14.97	0.125	Histamin 0.2 mg. hypodermically
9	11,200	12,220	1.001	13.44	9.92	0.088	5.81	9.73	0.080	
10	.....	10,170	1.002	12.96	9.85	0.097	4.92	7.10	0.070	Dried gland by mouth
11	.....	10,365	1.002	12.00	8.88	0.085	4.49	.....	.....	
12	.....	9,100	1.002	10.56	7.74	0.085	4.42	4.57	0.050	Dried gland by mouth
13	.....	8,735	1.001	14.78	8.93	0.102	8.49	10.09	0.115	
14	.....	13,425	1.001	16.00	.....	.....	6.45	.....	.....	
15	.....	10,245	1.001	12.16	.....	.....	3.60	.....	.....	Diarsenol
16	.....	9,020	1.001	11.20	.....	.....	5.24	.....	.....	
17	.....	9,405	1.002	11.52	.....	.....	3.20	.....	.....	
18	.....	10,385	1.002	10.08	.....	.....	5.04	.....	.....	
19	.....	11,940	1.002	.....	.....	.....	.....	.....	.....	Glucose tolerance and diarsenol

\* Some sodium chlorid was taken by the patient in the afternoon "to relieve the headache."

The rather frequent association of polyuria with pathologic changes (e. g., basal syphilitic meningitis) which might affect the hypophysis through compression, suggests that the relief of pressure might be accomplished by spinal puncture. In a case reported by Herrick<sup>1</sup> the polyuria was relieved by lumbar puncture; the effect continued during

a month of observation. However, there was apparently no increased pressure of the cerebrospinal fluid and only 5 c.c. were removed. The effect was manifested on the day following the puncture and still more so on the third day. Berblinger<sup>2</sup> reported a case in which the volume of the urine was diminished following an operation for cerebral decompression. Graham<sup>3</sup> presents a case in which the relief of pressure (caused by traumatic injury) was immediately followed by the cessation of the polyuria and other symptoms. Fitz<sup>4</sup> found that the lumbar

TABLE 2.—EFFECTS OF LUMBAR PUNCTURE

Day & Hour	Vol- ume	Sp. Gr.	NaCl		N		
			Per Cent.	Gm.	Per Cent.	Gm.	
8	810	1.002	0.080	0.648	0.074	0.595	Lumbar puncture
9	710	1.003	0.066	0.469	0.063	0.447	
10	560	1.002	0.083	0.465	0.071	0.400	
11	900	1.002	0.066	0.594	0.050	0.447	
12	875	1.002	0.054	0.472	0.051	0.447	
1	860	1.002	0.046	0.395	0.052	0.445	
2	865	1.002	0.037	0.331	0.051	0.457	
3	860	1.002	0.046	0.392	0.052	0.445	
4	935	1.003	0.042	0.393	0.054	0.504	
5	875	1.002	0.040	0.350	0.050	0.441	
6	910	1.002	0.041	0.373	0.061	0.544	
7	850	1.002	0.040	0.340	0.048	0.410	
	10,040			5.223		5.592	
7-7	8,365	1.002	0.066	5.650	0.053	4.557	
Day 4							
8	940	1.002	0.080	0.752	0.048	0.454	Specimen mixed in 7-7
9	885	1.002	0.046	0.407	0.038	0.327	
10	700	1.002	0.044	0.333	0.037	0.282	
11	840	1.002	0.050	0.420	0.037	0.312	
12	855	1.002	0.050	0.443	0.050	0.446	
1	610	1.002	0.029	0.178	0.067	0.410	
2	845	1.003	0.034	0.287	0.053	0.444	
3	900	1.003	0.027	0.243	0.047	0.442	
4	895	1.002	0.029	0.280	0.045	0.403	
5	818	1.002	0.029	0.226	0.047	0.384	
6	900	1.002	0.034	0.300	0.053	0.479	
7	890	1.002	.....	.....	.....	.....	
	10,085						
7-7	8,990	1.002	0.050	4.940	0.047	4.634	Analyses include 7 p. m.

puncture was ineffective in his case, and Barker and Mosenthal<sup>5</sup> report likewise. In Williams'<sup>6</sup> case, some relief was obtained, but for the day following the puncture only.

In our case, the polyuria was not alleviated by spinal puncture. In fact the twenty-four hour output of urine on the day of the puncture and on the following day was actually increased over the preceding observations (Tables 1 and 2). Nor were there any particular changes in the amounts and concentrations of the hourly specimens.

1. Herrick, J. B.: Arch. Int. Med. **10**:1 (July) 1912.
2. Berblinger: Verhandl. d. deutsch. path. Gesell. **16**:273, 1913.
3. Graham, E. A.: J. A. M. A. **69**:1498 (Nov. 3) 1917.
4. Fitz, R.: Arch. Int. Med. **14**:706 (Dec.) 1914.
5. Barker, L. F., and Mosenthal, H. O.: Tr. A. Am. Phys. **32**:233, 1917.
6. Williams, J. R.: Endocrinology **1**:312, 1917.

The subcutaneous injection of 1 c.c. of pituitary extract (Parke, Davis & Co., obstetrical pituitrin) resulted in a marked fall in the amount of urine secreted by our patient and an increase in the concentration. The maximum effect occurred during the third hour (Table 3, Day 5). A second injection early in the evening reduced the diuresis during the night. The administration of the pituitary extract at 8 a. m. the following morning brought the volume down to 37 c.c. for the fifth hour (Day 6). A final injection was given at 6 p. m. and was followed by an immediate fall to 55 c.c. for the succeeding hour. The 4,190 c.c. urine obtained this day indicate that the two injections per day were insufficient to control the diuresis completely.

TABLE 3.—EFFECTS OF PITUITARY EXTRACT GIVEN SUBCUTANEOUSLY

Day 5 Hour	Vol- ume	Sp. Gr.	NaCl		N		
			Per Cent.	Gm.	Per Cent.	Gm.	
9	815	1.001	0.075	0.611	0.045	0.367	1 c.c. pituitary extract at 10:20
10	860	1.001	0.073	0.628	0.040	0.343	
11	725	1.001	0.088	0.688	0.045	0.326	
12	75	1.012	0.562	0.414	0.553	0.415	
1	57	1.014	0.420	0.239	0.665	0.379	
2	92	1.007	0.340	0.313	0.406	0.374	1 c.c. pituitary extract at 7:30
3	150	1.007	0.270	0.405	0.364	0.546	
4	273	1.004	0.185	0.505	0.193	0.527	
5	170	1.003	0.185	0.315	0.207	0.352	
6	235	1.004	0.165	0.388	0.180	0.423	
7	255	1.003	0.125	0.319	0.165	0.421	
8	260	1.004	0.190	0.494	0.260	0.706	
8-8	3,967 1,145	1.006	0.300	5.269 3.435	0.241	5.179 2.757	

Each injection was followed by an immediate peripheral vasoconstriction and abdominal cramps. The patient's skin became moist. He could spit, and could swallow his food without washing it down with water as had been his custom. The intense thirst, general discomfort, pains in the back, etc., were immediately relieved. His appetite was marked, and more food was given him at his request on the second pituitrin day (Day 6). In addition to the large nitrogen intake, the greater voluntary consumption of salt on this day is of interest. The blood pressure was taken at 1 p. m. on the sixth day when the greatest antidiuretic effect was evident. The systolic pressure was 106 mm., diastolic 64 mm., and pulse pressure 42 mm.

The very positive but transient effects of pituitary extract injections are in accord with the findings reported in the literature.<sup>7</sup>

7. Von den Velden, R.: Berl. klin. Wehnschr. **50**:2083, 1913; Fermi, F.: Wien. klin. Wehnschr. **26**:1867, 1914; Römer, C.: Berl. klin. Wehnschr. **40**:108, 1914; Hoppe-Seyler, G.: München. med. Wehnschr. **62**:1633, 1915; von Konshegg, A., and Schuster, E.: Deutsch. med. Wehnschr. **41**:191, 1916; Bab, H.: München. med. Wehnschr. **63**:1685, 1721, 1758, 1916; Rosenbloom, J.: J. A. M. A. **70**:1292 (May 4) 1918; Motzfeldt, K.: Boston M. & S. J. **174**:644, 1916; Clausen, S. W.: Am. J. Dis. Child. **16**:195 (Sept.) 1918; Kennaway, E. L., and Mottram, J. C.: Quart. J. Med. **12**:226, 1919.

In connection with the questionable identification of histamin as the active principle of the posterior lobe of the hypophysis (Abel and Kubota <sup>8</sup>), it is of interest to note that tincture of ergot and "ergotin" have been used in the treatment of diabetes insipidus with some benefit (Futcher <sup>9</sup>). Again, Motzfeldt <sup>10</sup> found that a preparation of ergot had an inhibitory effect on diureses induced in rabbits, and he also obtained similar results with histamin and tyramin.

The administration of 0.2 mg. of histamin (Burroughs, Wellcome & Co.) has resulted in a definitely positive reduction of the volume and in an increased concentration of the urine (Table 4). As compared with pituitary extract, the results may be expressed relatively; while the pituitary extract increased the concentration of the sodium chlorid and the nitrogen of the urine six and fifteen times, respectively, the histamin effected a concentration of three and six times only.

TABLE 4.—EFFECTS OF HISTAMIN INJECTION

Day & Hour	Volume	Sp. Gr.	NaCl		N	
			Per Cent.	Gm.	Per Cent.	Gm.
9	480	1.001	0.092*	0.483*	0.057*	0.300*
10	570	1.003	0.092*	0.483*	0.057*	0.300*
11	350	1.003	0.112	0.392	0.098	0.343
12	105	1.008	0.320	0.336	0.372	0.391
1	300	1.002	0.090	0.276	0.123	0.370
2	710	1.001	0.080*	0.532*	0.087*	0.577*
3	650	1.002	0.080*	0.532*	0.087*	0.577*
4	430	1.002	0.144*	0.669*	0.101*	0.469*
5	510	1.002	0.144*	0.669*	0.101*	0.469*
6	480	1.003	0.136*	0.925*	0.070*	0.479*
7	880	1.002	0.136*	0.925*	0.070*	0.479*
7-7	5,960	1.003	0.136	8.133	0.073	4.353
8	580	1.004	0.108	0.626	0.061	0.358
	11,985			14.976		9.465

\* Average per hour for 2 hour period.

A general peripheral vasodilation immediately followed the injection; the subsequent severe headache and general prostration lasting until evening are seemingly characteristic of histamin (Popielski <sup>11</sup>) and are widely variant from the effects of the pituitary extract. The administration of the histamin caused so much discomfort to the patient that the experiment was not repeated.

8. Abel, J. J., and Kubota, S.: *J. Pharmacol. & Exper. Therap.* **13**:243, 1919; Dudley, H. W.: *ibid.* **14**:295, 1919; Jackson, D. E., and Mills, C. A.: *Lab. & Clin. M.* **5**:1, 1919; Hanke, M. T., and Koessler, K. K.: *J. Biol. Chem.* **43**:557, 1920.

9. Futcher, T. B.: *Tr. A. Am. Phys.* **19**:247, 1904.

10. Motzfeldt, K.: *J. Exper. M.* **25**:153, 1917.

11. Popielski, L.: *Arch. f. d. ges. Physiol. (Pflüger)* **178**:237, 1920.

The results are interpreted as indicating that histamin is not the active principle of the pituitary gland. However, the antidiuretic substance is probably some related compound, as suggested by Kennaway and Mottram. We understand that Rowntree has failed to duplicate the action of pituitary extracts in diabetes insipidus by injections of histamin.

TABLE 5.—EFFECTS OF DRIED WHOLE GLAND GIVEN BY MOUTH

Day 10 Hour	Vol- ume	Sp. Gr.	NaCl		N		
			Per Cent.	Gm.	Per Cent.	Gm.	
9	360	1.004	0.088	0.317	0.079	0.285	
10	500	1.005	0.088	0.519	0.097	0.584	
11	540	1.002	0.080	0.432	0.088	0.473	Dried gland, 3 grains by mouth
12	270	1.005	0.080	0.216	0.160	0.432	Dried gland, 3 grains by mouth
1	540	1.002	0.056	0.280	0.115	0.575	
2	360	1.004	0.056	0.202	0.094	0.338	Dried gland, 3 grains by mouth
3	710	1.002	0.048	0.341	0.066	0.684	Dried gland, 3 grains by mouth
4	165	1.007	0.150	0.248	0.220	0.362	
5	320	1.004	0.088	0.282	0.136	0.445	
6	120	1.007	0.104	0.125	0.253	0.304	
7	405	1.003	0.050	0.203	0.114	0.462	
7-7	5,470	1.002	0.068	3.720	0.084	4.595	
8	360	1.004	0.060	0.216	0.088	0.315	
	10,170			7.101		9.852	
Day 11							
8-10	820	1.002	0.048	0.394	0.072	0.587	
11	615	1.002	0.080	0.492	0.072	0.443	
12	350	1.004	0.062	0.322	0.095	0.331	
1	345	1.003	0.080	0.276	0.097	0.333	
2	520	1.003	0.090	0.468	0.085	0.444	
3	745	1.002	0.056	0.417	0.082	0.608	
4	465	1.002	0.066	0.397	0.092	0.430	
5	575	1.002	0.080	0.460	0.089	0.511	
6	285	1.004	0.060	0.151	0.116	0.331	
7	465	1.003	0.052	0.242	0.130	0.592	
7-7	4,850	1.003	.....	.....	0.084	3.874	
8	330	1.005	0.160	0.528	0.120	0.395	
	10,365					8.880	

Essentially negative results are reported throughout the literature as the result of administering pituitary preparations by mouth in diabetes insipidus. Barker and Mosenthal state that the administration of the extract of the posterior lobe by mouth in tablet form, even in fairly large doses, did not prove to be of value. Motzfeldt, however, was able to check the diuresis in one case by feeding the fresh posterior lobe of the ox. Kennaway and Mottram gave 1 c.c. of pituitary extract by mouth twice daily over a period of eight days with no appreciable lessening of the polyuria.

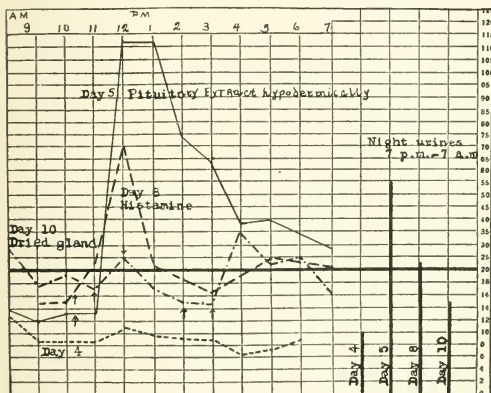
It is probable that the active substance of the posterior lobe of the hypophysis is destroyed in the alimentary tract. Thus, while Dale<sup>12</sup> failed to alter the activity of the extract of the gland by peptic diges-

12. Dale, H. H.: *Biochem. J.* 4:427, 1909.

tion in 0.2 per cent. hydrochloric acid for twenty-four hours, every active preparation of trypsin tried reduced the effects on blood pressure and urinary flow (Schäfer) practically to *nil* after a few hours.

There is a definitely diminished volume and increased concentration of the urine collected hourly as the result of giving by mouth comparatively large amounts of the dried whole gland (Table 5, Day 10), though the effect is not great. The continued administration by mouth of the dried whole gland (25 grains) over a twenty-four hour period on the twelfth day was hardly more favorable.

It is of interest to note that following the first subcutaneous injection of pituitary extract, the daily output of urine fell from over 15,000



Diabetes insipidus: hourly urine concentrations. The sum of the sodium and chlorin percentages are plotted as decigrams per 100 c.c. of urine.

c.c. to about 10,000 c.c., and the concentration relatively increased. There is undoubtedly a slight beneficial effect which persists for some days after pituitrin administration. That this may be manifest when pituitary preparations are given by mouth is indicated; exclusive of the days when pituitary extract was given subcutaneously, the least twenty-four hour elimination occurs on the thirteenth day.

Kennaway and Mottram conclude that the sum of the nitrogen and chlorin percentages in the urine must be proportional to a very large

fraction of the total urinary solids, since the sulphates, and in part the phosphates (as products of protein metabolism), will vary in the same manner as the nitrogen. Their curve shows a very close parallelism between the  $\Delta$  of the daily urines and the nitrogen plus chlorin in grams per cent. "When large amounts of sodium chlorid are given, the diuresis is so adjusted that the percentage of nitrogen plus chlorin in the urine remains unaltered."

Hourly concentration curves of the twenty-four hour urines of our case show this same constancy during the day except for a relatively greater concentrating power in the early morning hour, as shown in the accompanying illustration. The comparative effects of pituitary extract and histamin on the power of the kidneys to concentrate are brought out in a striking manner.

TABLE 6.—NITROGEN PARTITION AND EFFECTS OF PITUITARY INJECTION

Day	Food N. Gm.	Total N. Gm.	Urea N		Ammonia N		Uric Acid N		Creatinin N		Undetermined N	
			Gm.	Per Cent.	Gm.	Per Cent.	Gm.	Per Cent.	Gm.	Per Cent.	Gm.	Per Cent.
1	11.68	11.25	7.69	68.4	0.84	7.5	0.22	1.8	0.51	4.5	2.00	17.8
6	17.12	7.74	5.60	72.2	0.71	9.2	0.29	3.8	0.48	5.2	0.67	8.6
7	12.96	8.77	5.75	65.7	0.94	10.7	0.20	2.2	0.50	5.7	1.38	15.7

Pituitary extract injections, two doses, 1 c.c. each, were given Day 6.

Figures for the composition of the urine in diabetes insipidus are limited chiefly to the determination of total nitrogen and sodium chlorid as evidence of the concentrating power of the kidneys. The results for total nitrogen have been essentially normal. Hawk<sup>13</sup> has shown that the consumption of large amounts of water affects the nitrogen metabolism in normal persons; similar changes, at least, might be expected in diabetes insipidus. Table 6, Day 1, shows that high total nitrogen, ammonia nitrogen, and undetermined nitrogen figures obtain. A lessened elimination and a considerable retention of nitrogen occurred on the sixth day, the second pituitary extract day; the nitrogen partition on this day is more normal in character. On the post-pituitary extract day (Day 7), there was a tendency to revert to the picture for the first day. The first pituitary extract day (Table 1, Day 5) shows a low total nitrogen also. There was no creatinuria. Uric acid is rather high for a nonpurin diet, and is increased on the pituitary extract day despite the diminished water excretion.

Rosenbloom and Price<sup>14</sup> reported figures for the nitrogenous and mineral metabolism in a boy with diabetes insipidus.

13. Hawk, P. B.: *Biochem. Bull.* **3**:420, 1914.

14. Rosenbloom, J., and Price, H. T.: *Am. J. Dis. Child.* **12**:53 (July) 1916.



The figures obtained for the several blood constituents are given in Table 7.

There is hypoglycemia and a high uric acid content. Other constituents are normal.

Very high blood uric acid figures are reported by Hammett, Patten, and Suitsu<sup>16</sup> as a physiologic reaction to pituitary extract administration in nonendocrine cases. Socin and others have found that the  $\Delta$  and the sodium chlorid content of the blood serum are essentially normal in diabetes insipidus. Williams reports high blood fat and blood cholesterol in his case.

Blood glucose determinations (Benedict) on the nineteenth day before and two hours after the ingestion of 100 gm. glucose were 0.093 and 0.092 per cent., respectively; with the modified method (Table 7, note), the figures were 0.073 and 0.064 per cent, respectively. Urine specimens collected hourly were negative for sugar (Fehling).

TABLE 7.—COMPOSITION OF THE BLOOD (SUBSEQUENT TO PITUITRIN ADMINISTRATION)

	Day 15	Day 17	Day 20
Urea nitrogen.....	9.1 mg.	11.9 mg.	
Creatinin.....	0.6 mg.		
Uric acid.....	4.0 mg.	7.4 mg.	3.0 mg.
Plasma sodium chlorid*.....	64.4 mg.		
Glucose (Benedict), per cent. ....	0.079		
Glucose (modified Benedict)†.....	0.041		
Plasma proteins, per cent. ....	6.08		

\* 4 c.c. plasma, 10 c.c. water, and 7 c.c. saturated iron alum solution made up to 25 c.c., and heated in the boiling water bath. The precipitated proteins were filtered off. To the filtrate (17.5 c.c.), 2.5 c.c. of standard silver nitrate solution (Volhard-Arnold) and two drops of concentrated nitric acid were added, and 15 c.c. of this filtrate were titrated with the standard thiocyanate solution 5-fold diluted. The sample was not collected under paraffin oil.<sup>15</sup>

† After adding 0.25 c.c. of dilute sulphuric acid to the blood before precipitating with the sodium picrate-picric acid reagent, and using 1.1 c.c. of sodium carbonate solution for the reduction.

Sugar tolerance tests have been employed by Römer, Motzfeldt, Richter<sup>17</sup> and Schnabel and Gerhard.<sup>18</sup> A normal or increased tolerance is indicated by these observations.

The patient did not remain in the hospital long enough for a more complete study or for additional and satisfactory syphilitic treatment. But two injections of the diarsenol brand of arsphenamin were given, one the day previous to leaving the hospital. Indirect word was received from the patient subsequently that no relief from the polyuria had obtained.

15. Myers, V. C., and Short, J. J.: *J. Biol. Chem.* **44**:47, 1920.

16. Hammett, F. S.; Patten, C. A., and Suitsu, N.: *Am. J. Physiol.* **41**: 588, 1920.

17. Richter, G. J.: *J. Missouri M. A.* **13**:308, 1916.

18. Schnabel, T. G., and Gerhard, A. M.: *New York M. J.* **111**:812, 1920.

Contrary to earlier opinions, Elsner<sup>19</sup> states that he has not been able to control the complex in these cases by specific treatment. Römer and also Fitz report that syphilitic treatment had no noticeable effects in their respective cases.

#### SUMMARY AND CONCLUSIONS

A severe case of diabetes insipidus with chronic syphilis was studied.

The symptoms were not relieved by lumbar puncture.

The subcutaneous administration of pituitary extract (doses, 1 c.c. each, of the obstetrical preparation) was effective temporarily in increasing the concentration and reducing the volume of the urine, as reported by other observers. A normal twenty-four hour volume and concentration were not obtained.

Histamin (1 injection of 0.2 mg.) gave a similar but less effective result. It is probably not the active principle of the pituitary gland.

Desiccated whole pituitary substance in four 3 grains doses by mouth had a slight immediate effect.

On the day following the first injections of the pituitary extract and on subsequent and intervening nonpituitary extract days, there was a maintained decrease in the polyuria from over 15 liters to about 10 liters per day and a relative increase in the concentration of the urine.

Nitrogenous metabolism (over twenty-four hour periods) is affected in part as in the case of a normal person with a large water intake (Hawk). High ammonia, uric acid, and particularly undetermined nitrogen figures, were obtained; there was no creatinuria. As the result of pituitary extract injections, there was a lower nitrogen elimination with considerable retention, diminished ammonia and undetermined nitrogen, and a somewhat increased uric acid output; the nitrogen partition was more nearly normal.

Glycogenesis was not reduced. There was hypoglycemia. Blood urea, creatinin, plasma chlorids, and total plasma proteins were normal. The very high blood uric acid figures obtained may be explained as an effect similar to that of pituitary extract administration in nonendocrine cases.

We wish to thank Dr. F. H. Lamb of Davenport, Iowa, by whom the case was referred to Dr. C. P. Howard for study. The diets were calculated and prepared by Miss Gertrude Whiteford.

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19. Elsner, H. L.: *Monographic Medicine* 4:1123, 1916.

# INFLUENZA PANDEMICS DEPEND ON CERTAIN ANTICYCLONIC WEATHER CONDITIONS FOR THEIR DEVELOPMENT

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SAN FRANCISCO

## SYNOPSIS

Air pressure records (1826-1920) exhibit the fact that high pressure periods, lasting a number of years, vary with similar periods of low air pressure. Changes in solar activity harmonize with and apparently cause such pressure periods. Influenza pandemics and pneumonia epidemics develop only during high pressure periods. Influenza pandemics of 1890, 1891, 1918, 1919 and 1920 prove this fact as far as records are obtainable for the Northern Hemisphere and probably also for the Southern Hemisphere. All these epidemics come to a more or less sudden end following the advent of distinctly low air pressure. Records of cities in a highly diversified climate, as, for instance, California represents, prove that no meteorologic element, except air pressure, runs parallel to the development of influenza or pneumonia epidemics. Since it is definitely proven that these epidemics are a function of anticyclonic weather values, we must extend our laboratory work to an investigation of the physics of the atmosphere. The proposition is, whether the atmosphere during those epidemics acts as the carrier of a certain virus, or whether its physicochemical quality, changed during such weather periods, is the cause of influenza.

\* \* \* \*

The relation of climate or weather to health, and especially to the incidence of pneumonia and influenza epidemics, always has been a most difficult problem for the investigator. The people living on the continents experience a climate which changes almost hourly in temperature, humidity and other meteorologic elements. There is a constant movement of the air that surrounds us. On the continent of Europe and on the area of the United States the air is generally moving from the West to the East. This movement is subject to a change in its direction; for instance, by the occasional influx of gigantic masses of air, generally coming from a northerly direction, but also descending from considerable height. Such inflowing air may cover the entire continents and assemble there for a number of weeks, without any tendency to resume the easterly direction. As increase of air pressure is necessarily incidental to such air assemblage, and as the mechanical effect of such pressure has been considered negligible, the influence on health of this meteorologic factor has been generally disregarded in favor of tem-

perature and humidity as the principal factors affecting health. If we scrutinize the foundation for the latter assumption on areas of the continents which are not subject to any material change of temperature and humidity from summer to winter, as for instance, on the coast area of California, from San Francisco to San Diego, it becomes clear that the so-called "cold weather diseases" or respiratory diseases are not a function of temperature and humidity, but are dependent on certain high air pressure conditions. This fact, abundantly proven on such areas,<sup>1</sup> eliminates temperature and humidity as important factors. As humidity has lately been put into the foreground as a more important factor than temperature, it is of special interest that in such parts of the continents where humidity is very low we find exactly the same development of "respiratory diseases" as on very humid areas. For instance, the incidence of pneumonia epidemics in concentration camps of the U. S. Army from 1917 to 1919 proved that camps with a monthly relative humidity of below 50 per cent. had the same incidence as camps with a relative humidity above 80 per cent.; that camps in Southern California and Texas, with a maximum of sunshine, had the same incidence as those on the Atlantic coast. However, all of the camps in the United States were subject to the incidence of pneumonia epidemics, whenever they happened to be under the influence of certain high air pressure conditions.

Since the appearance of the influenza pandemic of 1889, we have had a number of references in literature<sup>2</sup> to the appearance of high pressure periods simultaneously with the outbreak of influenza. A study of such periods became imperative. Anticyclones are formed in the rear of extensive cyclones by the discharge of immense, cold masses of air into lower latitudes.<sup>3</sup> An area of high pressure results. If the cyclone ahead of this area retards its procession, then a more or less stationary anticyclone is formed. In its center the air is descending by gyration and flowing outward everywhere in its circumference. Its rate of progress is about 41 kilometers per hour in the United States and 25 kilometers in Europe (46 kilometers for the cyclones). Such an anticyclone may remain stationary, however, for from one to four weeks over the entire United States, or the entire area of Europe. Differing from these originally cold anticyclones there appear sometimes others of likewise long duration, which are dynamically warm from the beginning, and which appear to have their origin in the upper circulation of the atmosphere. They are of rather rare occurrence and extend probably into the stratosphere (from 5 to

1. Richter, C. M.: *J. A. M. A.* **36**:188 (Aug. 4) 1894.

2. Richter, C. M.: *J. A. M. A.* **51**:660 (Aug. 22) 1908; **57**:1964, (Dec. 16) 1911; Anders, H. S.: *Philadelphia M. J.*, Jan. 24, 1903.

3. Hann, J.: *Lehrb. der Meteorologie*, 1915, p. 624.

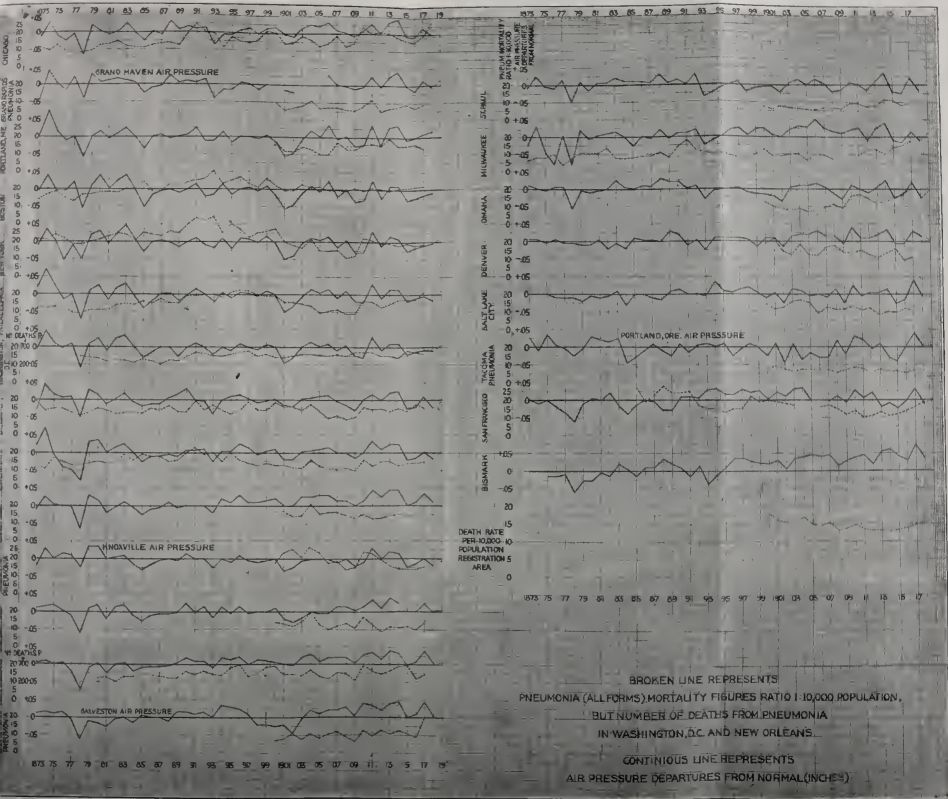


Figure 1



Continuous line represents air pressure figures, taken at 6 A.M. (Washington D.C. time) every day, reduced to sea level and standard gravity.  
 Weekly lines—give number of deaths from Pneumonia (all forms), and --- give number of deaths from Influenza and Pneumonia

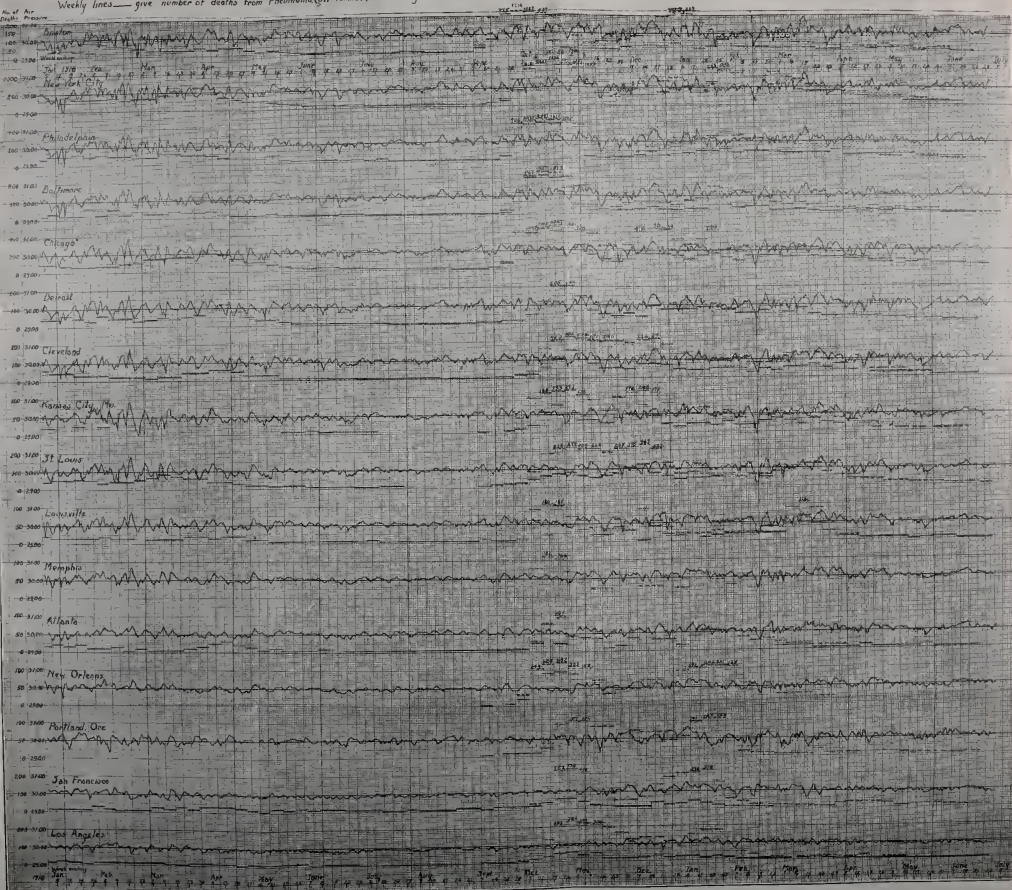
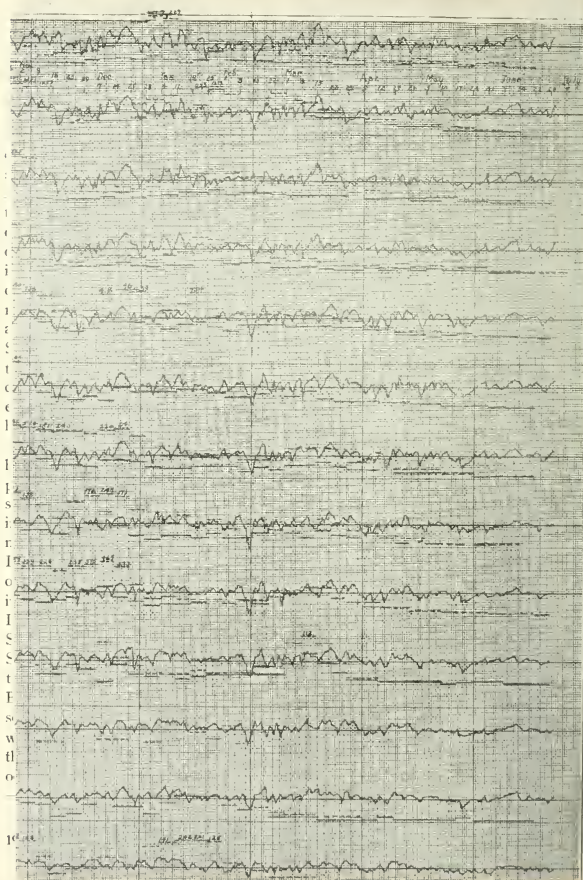


Figure 2

to sea level and standard gravity.

enzo ~~api~~ Pneumonia



9 kilometers). (The so-called troposphere extends from about 1 to 5 kilometers, and the stratosphere from 9 to 15 or more kilometers).

Our weather conditions do not depend, in reality, on cyclones and anticyclones, but on the great air currents in the substratosphere, which determine the dynamics of the atmosphere.<sup>4</sup> The entire weather system of the United States, for instance, according to Bigelow,<sup>5</sup> varies systematically with the variation of sun protuberances and sun spots. An increase of solar activity brings the cyclones into lower latitudes, increases the east drift of the upper air currents, lowers the temperature and increases the air pressure (lowers it at the equator). Koppen<sup>6</sup> declares that we possess in the eleven year sun-spot period the first directly proven period of weather conditions, even if not parallel to year or day. Naturally, this eleven year period must also be in direct relation to air pressure variations on our continent. Nansen<sup>7</sup> summarizes thus: In different groups of areas on the earth the meteorologic elements (temperature, rainfall, barometric pressure, etc.) fluctuate, or pulsate, so to speak, in time with one another, while in other groups of areas the fluctuations or pulsations are exactly inverted, and finally some areas show transition stages between the two. The result of all this is a very complicated picture of the meteorologic fluctuations. But by means of appropriate analysis we see that from this complicated and apparently chaotic set of fluctuations there arises a clear picture of the very intimate relation between all these variations, and the variations in the sun's activity. We have seen that even changes of very short duration in the sun's radiation (of heat as well as electricity) are distinctly repeated in our meteorologic conditions. The effects of the solar variations are probably transferred by means of variations produced in the distribution of pressure in our atmosphere. Changes in solar radiation probably first affect the higher layers of our atmosphere and thus create an unrest, which in turn is transmitted to the lower strata near the earth's surface. Such dynamic changes will produce different effects in different regions of the earth. Richter<sup>8</sup> demonstrated in 1892 this correlation of air pressure and sun-spot periods.

Anticyclones in the United States present four types:<sup>9</sup>

1. Appearing off the Pacific coast,<sup>10</sup> generally spring and fall; (a) off the coast of Washington and Oregon; (b) off the coast of California.
2. Alberta type (Southwestern Canada) west of the hundredth meridian.

4. Shaw, W. H.: *Meteorolog. Ztschr.*, 1914, p. 67.

5. Bigelow, F. H.: *Am. J. Sc.*, August, 1910.

6. Koppen, W.: *Meteorolog. Ztschr.*, 1914, p. 327.

7. Nansen, F.: *J. Washington Acad. Sc.*, March 4, 1918.

8. Richter, C. M.: *Meteorolog. Ztschr.*, August, 1892.

9. Bowie, E. H., and Weightman, R. H.: *Monthly Weather Rev.*, Supplement 4, 1917.

10. De C. Ward, R.: *Ann. Assn. Am. Geographers* 4: 1915.



3. Rocky Mountains—Plateau Region type.

4. Hudson Bay Type, east of the hundredth meridian, region of the Great Lakes.

During the years 1892 to 1912 (inclusive) 1,937 anticyclones and 2,597 cyclones entered the United States.

The following figures give the number of the different anticyclonic types registered during this period:

1. (a) North Pacific, 383.16; (b) South Pacific (California), 192.

2. Alberta, 947.

3. Plateau and Rocky Mountain Regions, 272.

4. Hudson Bay, 143.

Their average speed of progression was 22.7 miles per hour. "These anticyclones generally move east by south, whilst the cyclones move east by north inside the United States. The frequency of anticyclones is greatest in January and least in June. The Alberta Highs not infrequently in the winter months move almost due south to the West Gulf states."<sup>9</sup> As we see, nearly all of the anticyclones appear north of latitude 46° and west of the hundredth meridian. "Of 81 anticyclones of more than 787 mm. (31"), in America and Europe-Asia (1877-1844) one appeared in October, 8 in November, 34 in December, 29 in January, 4 in February and 5 in March."<sup>3</sup>

In Europe four types are recognized.<sup>11</sup> They are called according to origin:

1. Spanish.

2. Russian-Scandinavian.

3. Central European.

4. Iceland.

The Spanish anticyclone is part of the constant subtropical Atlantic Ocean High, central over the Azores. It extends northerly in summer, sometimes as far as Iceland, but its branches at other times reach Scandinavia on their path across continental Europe. The Azores High in some years may extend easterly to such an extent that one of the great, stable, dynamic Highs is created, locating over the area of Europe for many weeks. The Russian-Scandinavian Highs are typical continental anticyclones, having their nucleus in Siberia, Turkestan or China. Air pressure inside their area may reach 800 mm., while the Spanish type may reach 775 mm. The Iceland Highs probably originate in Greenland, while the Central European Highs appear to be parts of the Russian or Azores Highs.

In an extensive air pressure study, covering the years 1826 to 1885, Hann<sup>12</sup> demonstrates that periods of very high air pressure

11. Dreis, J.: *Meteorolog. Ztschr.*, Feb. 1, 1915.

12. Hann, J.: *Die Vertheilung des Luftdrucks über Mittel- u. Süd Europa*. Wien., 1887, p. 110.

appear only at great intervals. Such a period existed from 1832 to 1836 in Middle Europe, extending from Petersburg to Warsaw, to Hungary, Paris, Basel and Palermo. It was a period of enormously high pressure, not equaled again before 1885. However, Petersburg had very high pressure again in 1839 and 1840. Another fact elucidated by Hann was the existence of a period of distinctly low pressure extending from Warsaw to Palermo from 1851 to 1855. A long period of high pressure followed from 1856 to 1864. The years 1874 to 1878 represented a low pressure period. We have no reliable pressure data for the United States before 1873. It appeared to Hann that the maximum pressure progressed from North to South. Hann's table also suggests that the years from 1842 to 1847 were a low pressure period; from 1847 to 1851 being a higher pressure period, and an increasing pressure after 1880. Hann notes the existence of a continuous rise of pressure during January in all years from 1826 to 1885, while pressure during April declined. He finds that deviations of pressure from normal have the same intensity and the same general character over the entire area of Europe.

The same fact is exemplified over the area of the United States. It has been made a special study by F. H. Bigelow,<sup>13</sup> who found that:

The secular variations of the barometer from year to year are by no means accidental, but a phenomenon of definite proportions. The years of maximum pressure (over the United States) are 1874-75, 1882-83, 1890, 1896-97 and those of minimum pressure are 1878, 1884-85, 1893, with an interval of about eight years each. The years of depression seem to have a wider amplitude than the years of maximum. Between the successive large minima there is usually a large maximum broken in two parts by a minor minimum, as in 1876, 1881, 1889, 1895. These minor depressions are not so persistent throughout the entire United States as the strong minima, and in fact some years there seems to exist a powerful and persistent directive impulse, that really dominates the prevailing pressure. In seeking the causes of this phenomenon, one may suspect purely cosmical causes due to the variable solar output; indeed, these barometric variations do closely follow the variations in the sunspot frequency and the other products of the sun's variable activity. It is evident that we can now correlate the years which have similar secular variations and study them climatologically to see if there are any marked and prevailing features which characterize them.

Bigelow's study embraces the years from 1873 to 1899. Since then years of minimum pressure have been 1901, 1902, 1909 and 1915 with minor minima in 1905, 1907 and 1912. The maximum pressure years extend continually from 1903 to 1908 and then from 1910 to the beginning of 1915. The last increase begins at the end of 1917 and extends into 1920. The North Dakota Station, Bismarck, seems to act as the key to this long series of high pressure years, showing a rise of pressure from 1878 to 1919. It is the gate for the Alberta

13. Bigelow, F. H.: Rept. Chief of Weather Bureau 2: 1900, 1901.

Highs which enter the United States in that region and then sweep over the United States in a southerly and southeasterly direction. Figure 1 shows, in accordance with Bigelow's findings, that certain years of minimum or maximum pressure are very clearly indicated by each station of the chart, most conspicuously for 1878. As Bigelow remarks: "The residuals of that year are persistently minus, 0.05 inch, for each station of the United States: for 1883 they are persistently plus, about 0.02 inch. This means a relative reduction, or increase of air pressure, representing a weight of many million tons of air covering the United States."

If we follow the pneumonia mortality line in Figure 1 we are struck at once by the remarkable fact that the period of low pressure from 1875 to 1879 corresponds with a well marked trough in the mortality curve. The low pressure period from 1884 to 1885 also harmonizes well with a diminished pneumonia mortality. The 1893 Lows are generally followed by the mortality line in the same, or the following year. There is very well marked harmony between the two curves during the "Low" period of 1901-1902, likewise in 1909 and 1915. These are the principal "Low" periods. The United States curve also indicates low mortality during 1901-1902, in 1908-1909 and in 1914. It also gives an intermediate depression in 1905, which is likewise clearly indicated in the air pressure Low.

The principal air pressure maximum period in 1874-1875 harmonizes with the mortality peak in 1875. The general air pressure rise in 1879 is followed by the general rise of mortality, and both curves extend with this character during the High of 1882-1883. An irregular rise of both curves follows with an intermediate common peak at 1888. A more definite period of high pressure begins at 1890—the beginning pandemic—with peaks common also to the pneumonia mortality in 1890, 1891, 1893, 1895, 1896, 1897, 1899 and 1900, when the Low period appears. The general rise of pressure from 1903 to 1908 exhibits a greater common rise in 1903, still more in 1904, in 1907 and after the Low of 1908-1909 in 1910-1911. A following High period from 1911 to 1915, has common peaks at all cities, although of an irregular type. The United States curve has well outstanding peaks at 1900, 1904 and 1907. After 1915 we notice a general rise of both curves leading into 1918, when the new pandemic begins at the second half of that year, following a period of unusually low pressure at the beginning of 1918, which is for this reason only not accompanied by a distinctly high pressure line for that year. The United States curve likewise rises clearly since 1915. It is obvious, that any conclusions that might be formed from this chart, may have to be qualified in regard to the accuracy of the mortality statistics. We may accept the

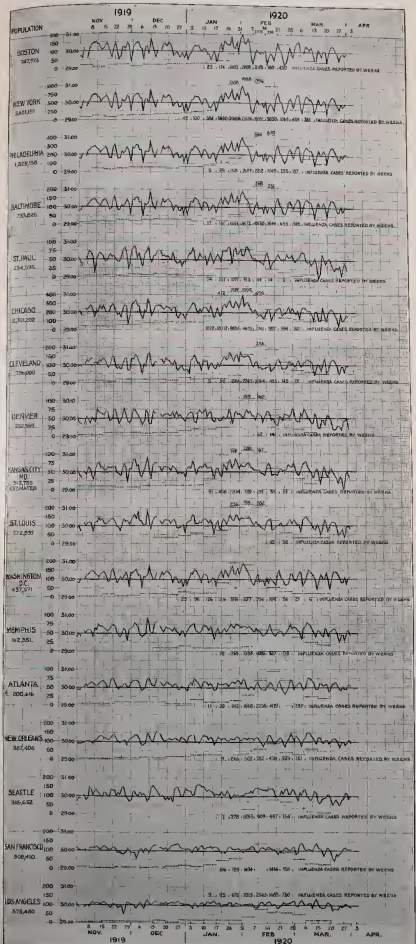


Figure 3



air pressure statistics as being practically free from great errors, but not those giving pneumonia mortality.

The census figures, for instance, differ in some cities materially from those of their health boards. Perhaps a reduction in the mortality line since 1900 is to be attributed somewhat to the policy of the "Census" to eliminate many cases of pneumonia, that had been classified under "primary cause of death." Great errors may also occur by the estimation of population. However, there remains a coincidence of gigantic departures of air pressure and gigantic pandemics. Our largest cities exhibit the same general tendency of rise and fall of both curves during definite periods of many years, and this by means of an annual air pressure curve that necessarily cannot elucidate the relation of cause and effect as a daily air pressure curve. Mean figures may be extremely misleading in certain years. St. Louis and San Francisco have the same mean annual temperature. The extremes of summer and winter in the former city permit of wrong conclusions in this comparison. Similarly low pressure periods at the beginning of 1918 and developing again toward the end of the year reduce the average pressure of the year sufficiently to conceal the unusual anticyclonic activity occurring between the two periods of low pressure. However, the general agreement in rise and fall of the two curves may at once suggest certain possibilities, as a rise of mortality following only certain types of anticyclones. For instance, so-called wandering anticyclones may constitute a positive departure of pressure in some years with a physiologic or pathologic influence on animal life different from that caused by the dynamic anticyclones as they appeared during the different pandemics. Only a careful perusal of daily air pressure conditions as presented on the other charts will give a proper understanding of possible cause and effect. The San Francisco charts are especially illuminating in that respect.

I may add here, that as Hann's<sup>12</sup> figures proved for the period from 1826 to 1885, likewise the evidence given by Richter<sup>1</sup> and Anders<sup>2</sup> corroborates the simultaneous appearance of unusually high barometric pressure during the influenza period from 1889 to 1897. The cities in Europe, generally, show the same years of minimum pressure, 1878, 1885, 1893, 1901-1902, and the same years of maximum as the United States, 1874-1875, 1882, 1889-1890, 1897-1898, 1905-1908. It should be noted here, that Lockyear<sup>14</sup> proved that in certain years the southern hemisphere is affected generally in the same months by high pressure conditions as is the northern.

Figure 2 shows that the different cities (Pacific Coast cities generally included) are exhibiting the same type of Low or High at the

14. Lockyer, N., and Lockyer, W. T. S.: *Proc. Roy. Soc. Lond.*, October, 1902.

same time—with a difference of, perhaps, only one or a few days. This uniformity is remarkable, and is equal to the uniformity found by Hann for Middle Europe. However, the extent of increase and decrease of air pressure in certain Lows and Highs seems extreme in the more northern cities, compared to those in lower latitudes. This is well explained by the record of the variability of the mean monthly pressure in different latitudes, following Hann.<sup>3</sup>

TABLE 1.—MEAN MONTHLY PRESSURES IN DIFFERENT LATITUDES

Latitude, degrees N. ....	60	56	52	48	46	43	38	32	20
Mean variability, mm. ....	3.06	2.92	2.58	2.34	1.95	1.80	1.48	1.00	0.40

The air pressure conditions existing before and during the last influenza pandemics in the United States are outlined as follows in the different Monthly Weather Reviews (U. S. Weather Bureau):

*August, 1918.*—"Pressure was high on several occasions on the West Coast, but there was no progressive movement (two stationary Highs near the 11th and 22nd of August). On the fifteenth rising pressure over northern Manitoba indicated the formation of an independent High." Pressure increased over Michigan, and on the nineteenth "this High was probably the controlling factor of the weather over the northern and central portions of the American continent." There was "a failure of the stationary areas of high pressure to progress eastward."

During *September* "there was entire absence of strong cyclonic action throughout the United States proper" and "the average barometric pressure was above normal through the whole country."

During *October* "the Highs were the dominating weather control of the month—there was more or less merging of North Pacific Highs with Highs which first appeared over the Canadian Northwest. The North Atlantic High was of greater intensity than usual."

During *November* "the Lows during the first half of the month, as in October, were decidedly lacking in intensity—the central portions of the country from the Atlantic to the Pacific were mostly under the influence of high pressure—after the fifteenth there was a marked increase in the intensity of the Lows—practically throughout the month pressure was above the normal off the California coast." Some of the Highs during this month disappeared rapidly. However, on the nineteenth "a marked rise in pressure had overspread Alberta. This rise advanced southward to Montana and to the West Gulf States and a branch of it reached Illinois and Mississippi on the twenty-third." "The Azores High was considerably greater in intensity than usual, and about 1,000 miles northeast of its usual position."

Tageswerte an Lufttemperaturmessung (per Woche) in NEW ORLEANS Louisiana

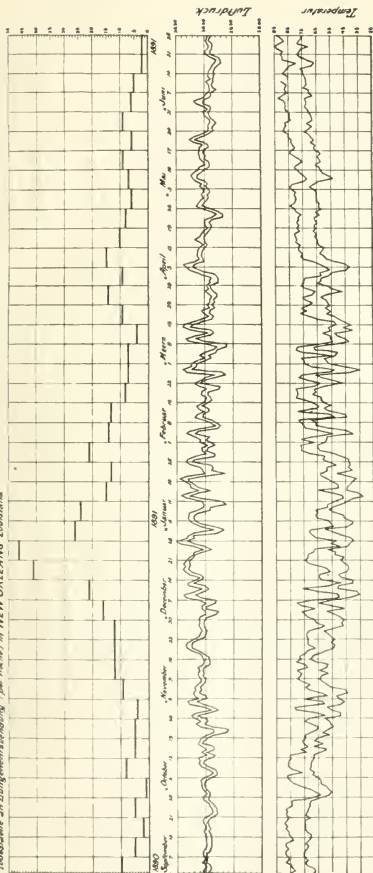


Figure 4



During *December* "the average sea level pressure was below the normal in the great central valleys and over the far Southwest, but elsewhere it was generally above normal." The Azores High was still similar to the November type.

During *January*, 1919, "the uniformly low pressure which had prevailed at Honolulu since December, 1917, gradually merged into a type of moderately high pressure and there was still further increase during January, 1919." In the United States "a general increase in pressure over middle latitudes—an almost constantly maintained High over the Plateau region—as a result the average for the month was well above the normal over the entire region from the Rocky Mountains westward, and from the Central plains eastward."

During *February* "pressure in the Northern Hemispheres, as in January, was high over the middle latitude of the continents and the Atlantic Ocean, 30.60 inches over parts of Siberia—a ridge of higher pressure apparently connects the continental Highs of northeastern Asia and the North American continent by way of Alaska and the Bering Sea." For the United States proper we learn that "the average pressure was below normal in practically all portions of the United States."

During *March* "there is a rather pronounced fall over the great continental Highs, amounting to 0.20 inch in Siberia and about half that much on the North American continent."

As the pandemic (Fig. 2) began about Sept. 1, 1918, in Massachusetts,<sup>15</sup> we find that this beginning was preceded by a development of stationary high pressure affecting the West Coast as well as the northeast of the United States during the second half of August.<sup>16</sup> We notice on the chart the entire absence during August and September of strong cyclonic action. The pandemic increased in severity until about October 12 (Boston); October 20 to 26 (New York, Chicago and San Francisco). The pressure likewise increased continuously and during October "the Highs were the dominating weather control." However, after October 5 Boston was experiencing development of Lows, while New York and the other cities had this deficiency in pressure one or two weeks later. The more or less rapid decline of the pandemic runs parallel to this development of low pressure on every city on the chart. About November 20, a second increase of

15. Pub. Health Rep., Sept. 27, 1918, p. 1626.

16. Sept. 17, 1918, report was made of the continued occurrence of a considerable number of cases of influenza at Boston and vicinity, where upward of 200 cases occurred on the day of the report, with a total of about 2,500 cases known to have developed during the outbreak. Sept. 17, 1918, the extensive prevalence of an influenza-like disease was reported at Camp Lee, Va.<sup>17</sup>

17. Pub. Health Rep., Sept. 20, 1918, p. 1604.

pressure begins, and it is followed by a second development of the pandemic in every city relative to this development. The morbidity apparently has its peak about December 20 and the mortality about two or three weeks later. This second increase of air pressure has its peak about December 19, somewhat later in Louisville and the

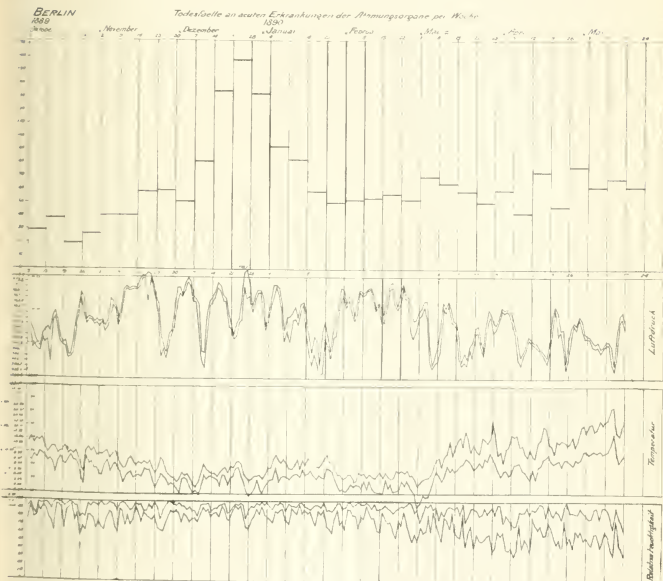


Figure 5

Pacific Coast. Following this, we find a marked intensity of low pressure continuing to February 14 and a few days earlier on the Pacific Coast. A new increase of air pressure during the middle of March is short lived on the Atlantic Coast, but of some duration at Chicago, Cleveland, Kansas City to Louisville, and we find in that area a moderate recrudescence of the epidemic.

No unusual features in weather or mortality develop until toward the end of 1919. In November, 1919, mean pressure in the Northern Hemisphere is characterized by a great continental High over northern Asia, relatively high pressure in a belt which engirdles the globe about 35 degrees north latitude." The weather in North America is largely controlled by the depth and persistence of the low pressure in the North Pacific—also by cyclones which form on the southern border of the semi-permanent High in middle latitudes—but cyclonic systems of pronounced character were notably absent. The average pressure showed the highest area extending as usual from the South Atlantic States northwestward to the northeast Rocky Mountains and Plateau regions with the maximum over Wyoming. Pressure was lowest over the Southwest."

During December, "the pressure at the Azores was considerably higher than usual." In the United States "the weather was distinctly under anticyclonic control, but during the third decade of the month lower pressure was the rule in practically all parts of the country. The excess of average pressure of December was least over the South Atlantic and East Gulf States and along the central and south Pacific Coast."

During January, 1920, "pressure over the United States alternated between low and high during the first and second decades, except in the Rocky Mountain Region, where it was high, while during the last decade it was almost continuously above normal throughout the entire country. Fifteen anticyclones entered the United States against nine, the average number for January—ten of them the Alberta type and four Plateau and Rocky Mountain region type. The most important features were the persistence of high pressure from the seventh to the nineteenth over the northern and central plateau regions—high pressure prevailed over the northern districts rising above 31 inches in eastern Montana. This high area moved along the northern border, but its influence was felt far to the southward. At the end of the month this high pressure area covered the northeastern States and some of the highest barometer readings ever observed in that region were reported. The average pressures for January were above normal in all portions of the United States and likewise in Canada as far north as observations disclose."

February opened "with a pronounced fall of pressure near the Aleutian Islands, where since January 10 it had been abnormally high. The extremely high area of the end of January moved rapidly into the Atlantic and was quickly followed by another that prevailed for several days from the Great Lakes eastward. During the same period pressure was generally high over the far West and low in the Southeast, where

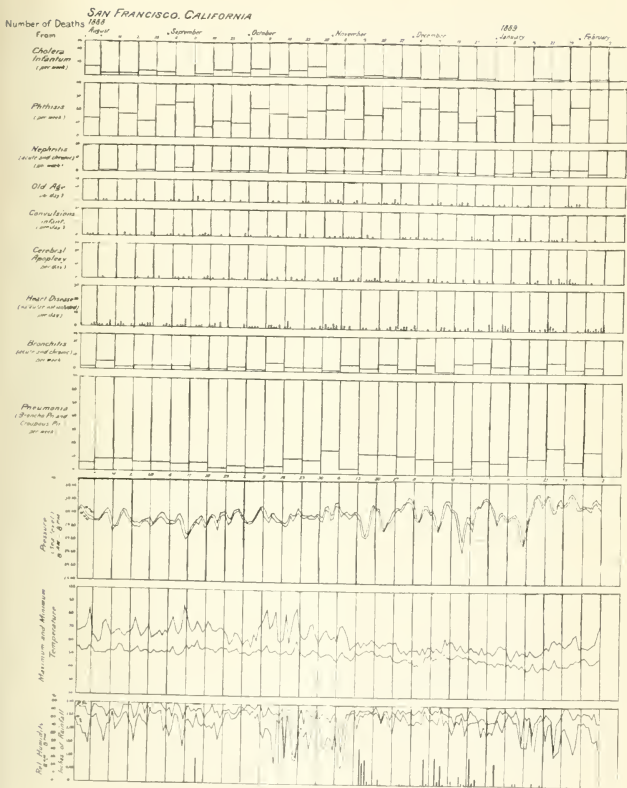


Figure 6

a Low moved northward from Florida up to New England. The average pressure of February was above normal over practically all the portions of the United States and Canada from the Mississippi and the Great Lakes westward to the Pacific, the departure increasing in the far northwestern districts, where at points it was the highest on record. In the eastern districts of the United States, as well as of Canada, it averaged considerably less than normal, particularly along the middle Atlantic Coast." Twenty cyclones entered the United States as against 11.9, the normal number, and ten anticyclones as against 7.8 normal.

March "was characterized by a remarkable series of cyclones that moved across the United States. Abnormally low pressures prevailed in every instance. An extensive and marked high pressure wave followed the storm of March 1 to 7, principally in the Southeastern States, but there were no other Highs of consequence—the averages of the month were below normal over practically all portions of the United States west of the Mississippi, north of the Ohio and over Canada." Eighteen cyclones entered against 11.8 normal, and ten anticyclones against 8.5 normal.

A general tendency to increase of pressure over the North American continent and a relative absence of cyclonic activity again characterize the weather of two months preceding the January, 1920 pandemic (Fig. 3). But instead of the gradual increase of high pressure we find, near the end of 1919, a more explosive increase of high pressure and during January, 1920, a gigantic High controlling the weather of the continent during the four or five weeks of the pandemic. The pressure condition during November and December, 1919, apparently helped to prepare the way, as we find a distinct gradual increase in the pneumonia mortality, beginning after the middle of November, notably in New York and Chicago. At the beginning of December, this influence is shared by almost all the cities on the chart, while the actual beginning of the pandemic, as indicated by the morbidity figures reported by weeks, may be traced directly to the relative development of very high pressure beginning about January 3 in the different cities.

A careful study of the individual cases in regard to the relative value of intensity of pressure and the partial interference by minor cyclonic action easily emphasizes the parallelism of the pandemic and the high pressure condition, which latter comes to an end about February 4 by a most intense cyclonic action. From the first week in January we note a very uniform pressure type for the cities on the Atlantic Coast and for the area from St. Paul and Denver to Chicago, Kansas City, Memphis and Atlanta. New Orleans participates in a general way, but the Pacific Coast again resembles the Eastern type.



which antedates the Pacific type by from one to two weeks. The Chicago type is at least one day ahead of the Atlantic Coast type and here, if we consider the report of influenza cases, is the first firm hold on the population—the other cities following in direct proportion to the development of the High over their area. The largest number of cases were reported for two weeks previous to the sudden collapse of the High, which occurred after February 4. Only Baltimore and Atlanta have a higher figure of cases for the week ending February 19, and San Francisco and Los Angeles likewise. Local difference in air pressure runs parallel to this difference. It is clear that the mortality line would lag behind from one to three weeks and longer.

Morbidity statistics relative to influenza are still far from ideal, but were, during the January, 1920 pandemic, probably more accurate than ever before. They were not sufficiently available before, except for a few states and cities.<sup>18</sup> Of these we find the highest number of cases reported:

TABLE 2.—INFLUENZA MORBIDITY STATISTICS

	For Week Ending	Cases
Maine.....	Oct. 26, 1918	6,754
Vermont.....	Oct. 21, 1918	6,949
New York City.....	Oct. 19, 1918	32,884
New Jersey.....	Oct. 19, 1918	71,215
Chicago.....	Oct. 19, 1918	12,183
Minnesota.....	Oct. 26, 1918	26,853
St. Louis.....	Oct. 19, 1918	4,043
Kansas.....	Oct. 19, 1918	14,892
Washington, D. C. ....	Oct. 12, 1918	9,708
Atlanta.....	Oct. 19, 1918	1,594
New Orleans.....	Oct. 19, 1918	17,070
Arizona.....	Oct. 19, 1918	3,530
San Francisco.....	Oct. 26, 1918	8,682

The report giving these figures states that "they are not exact or even more than approximately accurate." Only in Baltimore<sup>19</sup> has the attempt been made to trace cases of influenza back to August 1, 1918, but none are tabulated for August, while from September 1 an ever increasing number of cases is given until middle of October. A rather rapid decline begins about October 21. The outstanding fact is again the collapse of the epidemic following closely the cyclonic action, which begins with the second decade of October, 1918.

Even during the last pandemic mortality and morbidity statistics have been rather crude, but sufficiently complete in some cities to compare the time factor of the outbreak, peak and decline of the pandemic to the numerical values of atmospheric conditions, as measured by air pressure figures. The two factors easily explain the variation among cities in their different epidemiologic characters. Especially the Jan-

18. Pub. Health Health Rep., Nov. 8, 1918. p. 1914.

19. Pub. Health Rep., March 14, 1919.

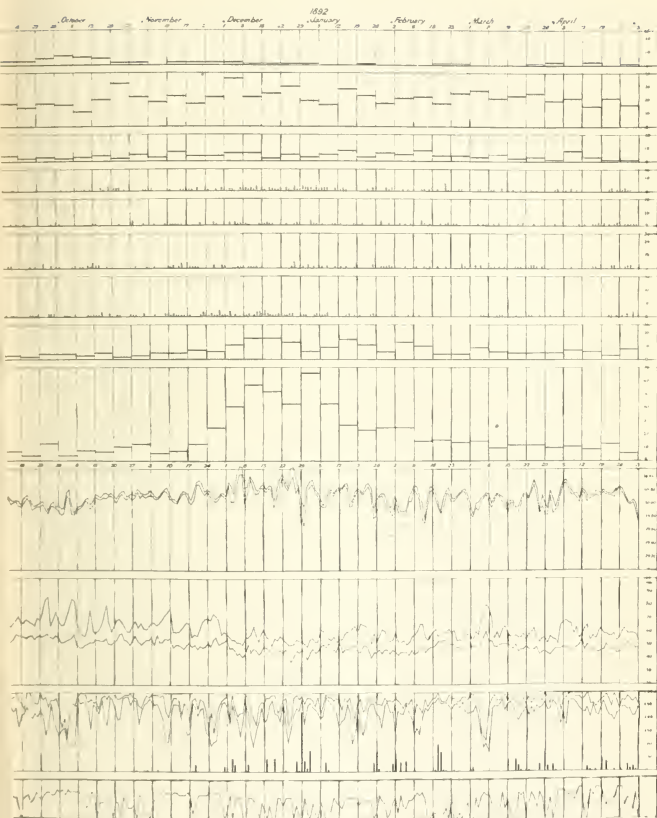


Figure 8



uary, 1920, pandemic proves the indisputable truth of their interdependence. Looking back to the 1890 pandemic we recognize in the examples of Berlin, New Orleans and San Francisco, the same decisive characteristics. They exhibit the same increase of air pressure toward the beginning, the same extreme High during the peak and the same collapse of the pandemic by the start of intense cyclonic action.

Comparing the San Francisco, New Orleans and Berlin charts for the pandemic 1889-1891, we find the following (Figs. 1, 2, 3, 4, 5):

TABLE 3.—INFLUENZA MORBIDITY, AIR PRESSURE AND CYCLONIC ACTION

	Mortality Peak or Increase	Air Pressure Peak or Increase	Cyclonic Action
Berlin.....	Dec. 21-28, 1889	Dec. 9-23, 1889	Dec. 23-30
Second wave.....	Dec. 30, 1889 to Jan. 17, 1890 and Feb. 1 to March 8, 1890	Dec. 25 to Jan. 17 and Feb. 1-22, 1890	Jan. 18-31 and Feb. 23 and following
San Francisco.....	Jan. 21-28, 1890	Jan. 7-21, 1890	Jan. 21-28
Second wave.....	Feb. 18 to March 18	Jan. 28 to Feb. 11, 1890	Feb. 11 to March 11
New Orleans.....	Dec. 14-28, 1890	Nov. 1 to Dec. 28, 1890	Dec. 29 to Jan. 11, 1891
Second wave.....	Jan. 28 to Feb. 1, 1891	Jan. 4-20, 1891	Jan. 20 and following
San Francisco.....	Dec. 8 to Jan. 5, 1891	Nov. 20 to Dec. 6, 1890	Dec. 27 and following

If we review the air pressure conditions during the recent pandemics, we recognize the identical anticyclonic action that characterizes the 1889 to 1891 pandemics. The first advent of those pandemics is heralded by a protracted continuous anticyclonic development, not interrupted by any cyclonic action. The first big pressure wave is followed then, as now, by one or two succeeding Highs, lasting again for weeks at a time. The intervals between them have cyclonic action. The mortality line has the same relation to the pressure types in both series of pandemics. Somewhat different is the pressure type at the time of the 1890-1891 pandemic at San Francisco, and of the January, 1920 pandemic in the United States. Both these types are not followed by succeeding waves. Both types have a more abrupt rise and fall of mortality and air pressure lines. The 1890 and the recent pandemic occurred during an advent of high pressure over our hemisphere, that in each case had been extending over some years previous to the outbreak of influenza and that apparently came to its highest and more specific development during or just ahead of the pandemic. I have charts that give the weekly mortality and daily air pressure for San Francisco from 1888 to 1904 (16 years) and for Berlin from 1887 to 1911 (24 years). The explosive appearance of influenza and pneumonia mortality are there confined exclusively to such periods as are marked by the advent of unusual anticyclonic action.

In addition to these facts we may consider the time relation of influenza pandemics and high pressure periods for middle Europe (since 1827) and for the United States (since 1873).

Of course, this secular coincidence of the pandemics and the high pressure periods does not enlighten us about the cause of an influenza pandemic or of an increase of pneumonia mortality, but it opens a window into the strange character of influenza. It certainly points to a distinct interdependence of the two, and points to the anticyclone as the decisive factor.

TABLE 4.—TIME RELATION OF INFLUENZA PANDEMICS AND HIGH PRESSURE PERIODS

Air Pressure Periods	Influenza and Pneumonia Pandemics
High 1831 to 1841, including "highest air pressure period (1832 to 1836) not equaled during the period 1826 to 1885." <sup>20</sup>	"Exceedingly intensive and extensive influenza period over the entire globe and consisting of the pandemics 1830 to 1832, 1833, 1836 to 1837." <sup>20</sup>
Low 1842 to 1847, beginning in some countries 1838.	No pandemics, but minor epidemics
High 1847 to 1851	Influenza pandemic 1846 to 1848, 1850 to 1851.
Low 1851 to 1855, distinctly low from Warsaw to Palermo	No pandemics.
High 1856 to 1864.	Minor epidemics 1855, 1857 to 1858. Irregular outbreaks 1860 to 1870.
Low 1874 to 1878, distinctly low pressure over United States and Europe.	Definite lowering of pneumonia mortality 1875 to 1878 over United States. Minor local epidemics 1873 to 1875, and 1879.
High and increasing 1881 to 1900 over the United States and Europe and continuing.	Local epidemics, principally in Russia, 1885 to 1888, also affecting the United States. Influenza pandemics 1889 to 1891 and irregular outbreaks to 1900
Low 1898 to 1902.	No epidemic of note.
High 1902 to 1920, definite period of increasing high pressure.	Pneumonia epidemics 1903, 1907, 1910, increasing incidence after 1915. Influenza pandemic 1918 to 1920, probably unequaled in severity.

The very source of the pandemics is found to be in that part of inner Asia or North America on the northern hemisphere where the centers of highest pressure are located on those parts of the continents. The air, carried by such dynamic anticyclones during their extreme development all over the two continents, is distributed with an anticyclonic velocity equal to that of our railroad trains.

The direction in which the air is carried out of the center of an anticyclone, varies, of course, with the location of the center. Suppose the center be at St. Louis, the air flowing out of the center would be carried by northwesterly winds toward Boston, by northerly winds to the middle Atlantic Coast, by northeasterly winds to the Gulf States, by easterly winds toward New Orleans and Texas, by southeasterly winds toward the Pacific Coast. Hann<sup>21</sup> summarizes thus: "The air circulation in the dynamic barometer maxima of the United

<sup>20</sup> Leichtenstern, O., and Sticker, G.: *Influenza*, Ed. 2, Wien, and Leipzig, 1912.

States, therefore, consists (1) of a true downward directed gyration near its center and extending about 500 kilometers outward; (2) in its outer circumference the motion everywhere has an outward direction and represents a forced rotating motion similar to a whirl in a stream." It is also stated by him that the barometer minima do not supply the air that enters the maxima above, as they do not reach to such height. The distance of the center of a dynamic anticyclone from that of a cyclone is generally about 2,000 miles in the United States and often more than that in Europe.

It is clear that only a most careful study of the daily weather maps will explain the actual air conditions in a certain district relative to a dominating influence of a High or Low. Furthermore, only such study will inform us whether a High is of the quickly wandering type or of a stationary dynamic character. Only continuous crowding of air over vast parts of the country, for instance, over the entire United States or over Europe, lasting quite a number of weeks, seems to carry the character that increases pneumonia mortality severely and paves the way for or starts a pandemic. As we have no special sense for electricity, nor for air pressure and its variations, we do not become aware of the differences that exist in the air we breathe during changes in those factors. It seems reasonable to consider the possibility that during the development of such unusual high pressure conditions, the physicochemical nature of the atmosphere that reaches our lungs has been altered in such a way that it may affect us more or less disastrously. Or, we may be induced to suppose that such air has become the carrier of a virus. The air of an anticyclone has been descending from a 10 to 20 kilometers height and naturally has been differently qualified during different solar activity. As soon as low pressure sets in, which carries the anticyclonic air away from us, influenza and pneumonia decline. It is difficult to harmonize this behavior with a bacteriologic origin of those diseases.

If we assume that the atmosphere acts as carrier of the cause of influenza, we are facing similar difficulties, as when we were forced by certain facts to assume that the water acted as carrier of the cause of typhoid fever and cholera. Now we know that infection of water is the most common source of widespread epidemics, originating in the contamination of a well or spring. Such epidemics are often as "explosive" as the pandemics. But how can infection be carried by the air, except with dust? But why do we insist on a virus, on an infection as the cause? Certainly only for sake of an analogy, that at best can be only a partial similarity. There is, however, a greater similarity between the march of the pandemic and that of the dynamic anticyclone. Both reach ships on the ocean, islands, distant camps that had

been as far removed from the pale of civilization as the North Pole. Is there, perhaps, a special physicochemical quality imparted to the air we breathe during a pandemic, imparted, for instance, by the radiant energy of the sun, by radioactivity, by ozonization? Lenard and Ramsauer<sup>21</sup> define the principal effect of the solar output on the atmosphere: First, the development of ozone "welche ziemlich tief herabreicht, weil sie schon durch schwach absorbierbare Strahlen bewirkt wird." Second, the continuous creation of fognuclei in the upper atmosphere. ("Amonnitrat und Nitrit aus dem lichterzeugten Ozon und dem Ammoniak der Luft, wahrscheinlich auch Wasserstoff-superoxyd aus Wasserdampf.") Third, continuous creation of carriers of electricity.

W. J. Humphreys<sup>22</sup> says: "One would expect to find an appreciable amount of ozone in the upper atmosphere, but, owing to its unstable nature and its great power of oxidation, very little near the earth. Only traces of ozone are found in the lower portions of the air and when there is much moisture and the temperature is high the amount is vanishingly small. On the other hand, Augstrom, by examining the absorption bands in the solar spectrum, has detected the presence of a very considerable amount of ozone, which must be in the upper air." "Ozone is produced by the action of ultraviolet radiation on cold dry oxygen; its amount, therefore, must vary with the amount of ultraviolet radiation sent out by the sun and this is a variable quantity." "Besides ozone is abundantly produced by the action of silent electric discharges; therefore, the amount of ozone in the atmosphere, since it results from the action both of auroral discharges and of ultraviolet radiation, will vary with their increase and decrease. The increase we should expect in the higher latitudes, where the auroral discharges occur. The equator to pole circulation of the upper atmosphere, and the paralleling of magnetic lines of force by auroral discharges, might very well lead to a greater amount of ozone in the upper air of temperate and polar regions than in that of the tropics."

The amount of ozone found in the air we breathe has repeatedly been estimated to amount to more than 1 part in 700,000 parts air. The effect of ozone on the respiratory organs has again lately been investigated. Jordan and Carlson<sup>23</sup> summarize the results of their research work, in part, as follows: "Human beings are injuriously affected by amounts of ozone far less than are necessary to produce bactericidal effect, and there is no evidence for supposing that a quantity

21. Lenard, P., and Ramsauer, C.: Sitzungsberichte der Heidelberger Academie der Wissenschaften, Abh. 24, 1911, p. 42.

22. Humphreys, W. J.: Astrophysical J. **32**: No. 2.

23. Jordan, E. O., and Carlson, A. J.: Ozone, J. A. M. A. **61**:1007 (Sept. 27) 1913.

of ozone than can be tolerated by man, has the least germicidal action. In concentrations that appreciably affect man, ozone appears to have uniformly an injurious action. This action is primarily on the respiratory passages—irritation of the sensory nerve endings, and irritation, corrosion and depression of the epithelial cells. The depression and drowsiness produced by ozone are due to the intense irritation of sensory nerve endings (vasomotor effect) in the respiratory tract, as well as to the secondary effects of the change in the activity of the alveolar epithelium. Nor can we accept the suggestion of Hill and Flack, that small amounts of ozone may be of therapeutic value in certain diseases of the respiratory tract by reason of the hyperemia following the ozone irritation. The ozone irritation leads to intense hyperemia of the respiratory tract, . . . The cells injured by ozone are probably more readily invaded by bacteria and have less than normal power of healing despite the hyperemia. The physiology of ozone points to the conclusion that the use of this poisonous gas as a therapeutic agent is either valueless or injurious." As these authors say: "The cardiac and vasomotor changes on exposure to ozone have not been extensively studied." "Here we have as an effect of exposure to ozone, generally considered harmless, symptoms as headache, sore throat, pain in the chest, intense irritation of the respiratory tract, and even if prolonged exposure to ozone should prove harmless to the robust person, what about the unfortunate person whose lungs have only slight power of resistance? Concentrations of ozone of 1 part per million parts of air are certainly injurious, but it does not follow that the weaker concentrations of ozone are proportionately injurious."

In addition to this research work we should consider the "studies of the respiratory inflammatory processes initiated by the inhalation of toxic gases" (used in modern warfare) made by Winternitz, Wason and McNamara.<sup>24</sup> They state that "the pathology produced by the inhalation of these poisonous vapors is analogous to that found in influenzal pneumonia." Their conclusions contain the following: "A basis for the interpretation of the respiratory lesions of influenza is offered by the analogous changes in the respiratory tract initiated by the inhalation of poisonous gases. The respiratory lesions are dependent primarily on the damage produced by the true etiologic agent and the systemic capacity to compensate, and only secondarily on invasion by the bacterial flora of the mouth and inspired air."

These findings gain in importance by the general agreement of clinicians that the influenza infection is carried directly into the respiratory tract. D. Symmers<sup>25</sup> concludes thus; "From the opportunity

24. Winternitz, Wason and McNamara: *The Pathology of Influenza*, Yale University Press, 1920.

25. Symmers, D.: *J. A. M. A.* **71**:1482 (Nov. 2) 1918.

that I have had to observe at necropsy and in the living patient, it appears to me to be probable that the prevailing pandemic of influenza is attended by pneumonic lesions from the beginning. Moreover, the distribution of the pathologic changes in the lungs is such as to suggest that the infection is introduced by way of the respiratory tract. . . . In those cases in which death has occurred twenty-four or thirty-six hours after the development of detectable pneumonic signs, it is scarcely conceivable that the massive solidification of the lungs could have taken place with corresponding rapidity. The suggestion naturally follows, that every case of pandemic influenza should be regarded from the outset as pneumonic."

Park<sup>26</sup> writes: "Epidemic influenza is a disease primarily attacking the respiratory tract." Conner<sup>27</sup> writes: "In the present epidemic there has been, for all practical purposes, only a single type—the respiratory." Kinsella<sup>28</sup> says: "Whatever the cause of the disease may be, it is clear that this agent is one to which the body is not accustomed." McLaughlin<sup>29</sup> concludes: "These indications suggest—either that in the great pandemic we were dealing with a new and entirely different disease, or that the immunity conferred by an attack, if any, was of a very fleeting character." Of course we could not acquire immunity from exposure to an irritating gas similar to ozone. The great clinician Ziemssen wrote many years ago, alluding to epidemics of influenza: "After all we cannot but assume that there must be general conditions, which appear and disappear simultaneously in great expanse of space. Of what nature these influences may be is perfectly dark. We would not be forced to think of miasm or contagion. We are more led to believe that fluctuations of other conditions, extending over great areas of the surface of our globe at the same time furnish an analogy."

#### CONCLUSIONS

In conclusion we should consider the following facts:

1. The assumption, that the propagation of influenza is analogous to that of an infectious disease, has so far no foundation in fact. We have no proof that influenza is caused by bacterial infection. The cause of influenza is still unknown. We have not succeeded in inoculating influenza from person to person; we cannot transmit it experimentally. A "drop infection" from person to person has likewise not been proved. Frost<sup>30</sup> believes in "contact in the broad sense" and

26. Park, W. H.: *J. A. M. A.* **73**:318 (Aug. 2) 1919.

27. Conner, L. A.: *J. A. M. A.* **73**:321 (Aug. 2) 1919.

28. Kinsella, R. A.: *J. A. M. A.* **72**:717 (March 8) 1919.

29. McLaughlin, A. T.: The Shattuck Lecture, Boston M. & S. J., July 1, 1920.

30. Frost, W. H.: *J. A. M. A.* **73**:313 (Aug. 2) 1919.

adds: "As regards preventive measures, the efficacy of those carried out—is not proved." Howard and Love<sup>31</sup> state that, "in U. S. Army Camps, where all accepted measures for the prevention of the spread of respiratory disease (during the pandemic) were vigorously enforced, the incidence of the disease apparently was as great as in other camps where such measures were less rigidly and effectively applied." Transmission of influenza is more logically explained by an air which may carry in infective virus or a poisonous gas, an animate or an inanimate agent, into our lungs and which naturally has free access everywhere. We cannot guard ourselves against such air, except by masks, which would nullify the bad effect of such air. The research work describing the effect of inhalation of ozone and warfare gas proves that the pathology of influenza can readily be explained by the assumption that a poisonous gas is the cause of the pandemic.

2. Atmospheric conditions that are characteristic, we could as well say pathognomonic, for influenza and its spread are well defined. The cycles in which the pandemics alternate with periods of relative quiescence are distinctly covered by the cycles of high air pressure periods during and before the pandemics and of low air pressure periods following them.

3. The first appearance of influenza cases in a pandemic, and the full development of the latter, are geographically in direct relation to the appearance and development of certain anticyclonic conditions. The successive seizure of great districts of the continent invariably originates in one or the other center of great anticyclonic action on the globe, as in inner Asia, Bokhara, and in Canada during the 1890 pandemic, and as in the region of the "Canary Island High" (Spanish influenza), and in Canada during the 1918 pandemic.

4. The influenza pandemic extends, spreads in the same direction and with the same velocity as the great anticyclone spreads from its center over a continent. In the United States therefore, it generally attacks first those districts that lie in the path of the Alberta type or the Hudson Bay type.

5. The prepandemic weather, as the charts prove, remains for a long period free from any cyclonic action. It is the forerunner of the coming avalanche of atmosphere.

6. Increases of influenza morbidity preceding a great pandemic are always in harmony with similar increases of an anticyclonic type of weather.

7. As the period of very high pressure of from 1830 to 1840 was synchronous with the greatest pandemic before our times, similarly, the 1890 and 1918 pandemics were heralded by an ever increasing air

31. Howard and Love: *Influenza*, *Mil. Surg.* **46**:522 (May) 1920.

pressure since 1878, reaching the highest figures only during the period of the last pandemic, as the Bismarck pressure line so well illustrates in Figure 1.

8. The anticyclonic weather conditions for some weeks before and during the prevalence of a pandemic are almost stereotyped for every city on the charts. The usual type for the United States is the Alberta type. The gigantic masses of air that it whirls and spreads over the country in a southerly and easterly direction with the velocity of a fast train, are represented by the more or less extreme positive departures of the air pressure from normal in the most typical manner in every city. Distinct cyclonic action is, then, missing in every single instance, and the only type in evidence is prolonged high pressure for a longer period, as in September and October, 1918, or for a shorter period of highest air pressure, as in January, 1920.

9. Likewise, we find in a stereotypic fashion the beginning of a decrease of morbidity in every city following the first well marked cyclonic action. As the anticyclonic period is common to the entire United States, proportionate only to the time necessary for the spread of its masses of air, likewise, the cyclonic action, when it arrives, puts its stamp on every city almost on the same day.

10. Extraordinary proof of the interdependence of the pandemic and an extreme high pressure period occurs in January, 1920. The beginning of both is clearly defined and the decrease of morbidity appears in direct relation to cyclonic action, beginning in the first week of February.

11. This interdependence gains additional value by the research work on prolonged exposure to ozone and other poisonous gases and the injury to the respiratory tract caused thereby. In fact, it is clear that the symptoms caused by inhalation of such poisonous gases resemble the influenza symptoms perfectly.

12. We have reason to assume that air of some anticyclones contains ozone in unusual quantity as a product of unusual solar output. If we hesitate to deduce that ozone is causative of influenza because its odor and the gas itself has not been detected in the air we breathe during a pandemic, we must admit that no attempt has been made to find it.

Of course some degree of speculation cannot be avoided if we seek for any theory to guide us in the labyrinth of influenza. The possibility of its spread by the atmosphere is consistent with the facts. It has the merit that it leads us to an experimental study of the air, and it gives us ozone as a guide. A second Schoenbein may arise and find a chemical body, similar to ozone, or we may extend Haldane's research work, which suggested that the rate of supply of oxygen to



the tissues by the blood in the systemic capillaries in the lungs is insufficient in influenza for the normal processes of life.

We cannot, after the presentation of the foregoing facts, escape our duty to demand a critical analysis of the air during the different air pressure conditions and especially during the epidemics of the respiratory organs. Furthermore, we have achieved the very important practical gain that we may predict an increase in pneumonia morbidity whenever an extensive anticyclone is approaching any territory in question, and we have a warning of a coming explosiveness of morbidity in general whenever the magnitude of the approaching anticyclone warrants it. The necessary information, easily given by the Weather Bureau, would make a suitable preparedness possible to meet the emergency. A failure to recognize this fact would seem to involve a great responsibility.

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#### SPIROCHETAL PULMONARY GANGRENE

Drs. Fishberg and Kline, authors of the paper with the above title, published in the *ARCHIVES OF INTERNAL MEDICINE*, January 15, 1921, p. 61, request the addition of the following paragraph to their paper:

The occurrence of fusiform bacilli and spirochetes, not only in the exudate over the gums but also in the gangrenous lung tissue, lends support to the belief that this is a case of aspiration pneumonia followed by pulmonary gangrene in which innumerable mouth organisms, Vincent's spirochetes and fusiform bacilli from the gingivitis were aspirated into the lungs, the mouth organisms producing the widespread consolidation and the spirochetes the associated gangrene.

## METABOLISM IN PELLAGRA: A STUDY OF THE URINE

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It is now well established that diet, according to its qualitative and quantitative nature, plays a most important part in the prevention, causation and cure of pellagra. Certain types of diet have been proved experimentally to be provocative of pellagra,<sup>1</sup> while in the Pellagra Hospital the treatment of the disease has been absolutely dietary.

Considering the part that diet, good or bad as the case may be, plays in pellagra, it would seem that whatever new facts are added to our knowledge of metabolism in pellagra would decidedly be worth while, particularly in view of the fact that the investigations of metabolism in this disease have not been extensive.

Camurri appears to be the first to have made a comprehensive study of metabolism<sup>2</sup> in pellagra. His work dealt particularly with the mineral metabolism. He states that the diet of the Italian pellagrins is lacking in sodium and calcium. Camurri's work included, also, a study of the composition of the diet, of the urine, and feces of pellagrins subsisting on mixed diets and on diets composed largely of corn. Balances were obtained for nitrogen, fat and salts in comparison with those of normal individuals on similar diets. In pellagra he found an increase in the excretion of chlorin estimated as sodium chlorid. Nicolaidi and Grillo<sup>3</sup> found a decided negative mineral balance in active pellagra. Myers and Fine,<sup>4</sup> in their extensive investigations of metabolism in pellagra, found that the ability of individuals suffering from pellagra to utilize the various foodstuffs was but slightly, if at all, below the normal.

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1. Goldberger and Wheeler: Experimental Pellagra in the Human Subject Brought About by a Restricted Diet. *Pub. Health Rep.* **30**: No. 46 (Nov. 13) 1915; *Bull.* **120**. Hyg. Lab. Washington, 1920.

2. Camurri: *Atti del quarto Congresso Pellagrologico*, Italiana, Udine, 1910, p. 67.

3. Nicolaidi and Grillo: *Tr. Nat. Assn. for Study of Pellagra*, Triennial Meeting, Columbia, S. C., 1912, p. 127.

4. Myers and Fine: *Am. J. M. Sc.* **145**:705, 1913.

Nitrogen balances with different diets were likewise studied by Hunter, Givens and Lewis<sup>5</sup> at the Pellagra Hospital. They conclude that "A diet providing 2,500 calories and containing 15 gm. nitrogen (of which 11 gm. are in the form of animal protein) is not only likely to promote the recovery of the pellagrin from an acute attack but is adequate to meet all the requirements, for maintenance and repair of his convalescence."

The frequent occurrence of gastric anacidity was noted by Johnson,<sup>6</sup> Ceconni,<sup>7</sup> Niles,<sup>8</sup> Myers and Fine, Hunter, Givens, and Lewis, and the presence of an excessive quantity of indican in the urine has been reported repeatedly, especially in the urine of American pellagrins. Myers and Fine concluded that the indicanuria is excessive in the cases with gastric inefficiency. Hunter, Givens, and Lewis, however, show that gastric inefficiency is only one of the factors involved in indican formation and that a very important factor is to be found in the patient's diet—the tendency to excessive indican formation being greater on a meat diet. They show further that the existence of pellagra is compatible with any degree whatever of indican production, even none at all and that indicanuria, undeniably a common feature of the disease, is by no means an essential one.

That indicanuria is not an essential factor in pellagra is shown also by the findings of Goldberger and Wheeler. Thus, in 1915 Goldberger and Wheeler<sup>1</sup> showed that pellagra could be produced experimentally in previously healthy human subjects by feeding a restricted one-sided mainly cereal diet of the type found to be associated with a high incidence of pellagra. The urine of their subject contained little if any indican while they were on the pellagra producing diet.

In the work herein described, a survey of the urine of pellagra patients was made as soon as possible after the patient's admission to the hospital and in some cases at the time of applying for admission to the hospital and before actual admission. Attention was paid to the variation in normal constituents, the presence of physiologic bases, and the presence of abnormal constituents.

Once started, the variation in normal and abnormal constituents was followed from the acute highly erythematous stage to the stage with a high degree of improvement or discharge from the hospital as recovered. In some of the lines of work started the results are fragmentary because of loss of personnel on account of the war. In this paper, however, are reported results of a study of the specific gravity, volume, total nitrogen, ammonia, creatinin, urea and uric acid.

5. Hunter, Givens, and Lewis: Bull. 102, II, Hygienic Lab. U. S. P. H. S., 1916.

6. Johnson: South. M. J. 4:578, 1911.

7. Ceconni: Gazz. d. osp. 32:77, 1911.

8. Niles: Pellagra, 1912, p. 77.

The methods employed were: for total nitrogen, Kjeldahl; for ammonia, Folin's <sup>9</sup> method as modified by Steel <sup>10</sup>; creatinin by Folin's method <sup>11</sup>; uric acid by the Folin-Shaffer <sup>12</sup> method; urea by Folin and Denis' method <sup>13</sup> using jack bean as a source of urease, and a reaction temperature of from 50 to 55 C. The urine of four normal persons was tested in a similar way at the same time.

Except for short periods, the normal individuals were under uncontrolled conditions with great variation in diet and with a mode of living quite different from that of the patients. Accordingly, considering that metabolism is more or less an individual question, it was concluded that the best control for the patients in active pellagra is the same patient at or about the time of discharge, when they showed no sign or symptom, which, in the judgment of the medical staff, would indicate a pellagrous condition. Much emphasis is put, therefore, on the comparison of data obtained just after the patient was admitted to the hospital and the data obtained just before the patient was to be discharged.

The patients in the hospital in 1917 were good cases of pellagra. The treatment in the hospital of uncomplicated cases, the only kind considered in this study, was entirely dietary. Two types of diet were employed during 1917, diet G and diet B as follows:

TABLE 1.—TYPES OF DIETS GIVEN PELLAGRINS

Diet G				Diet B			
	Gm.	N	Calories		Gm.	N	Calories
Loaf bread.....	300	4.02	864	Loaf bread.....	300	4.02	864
Butter.....	45	0.034	356	Butter.....	45	0.034	356
Corn meal.....	50	0.670	190	Corn meal.....	50	0.670	190
Hominy grits.....	50	0.638	181	Eggs.....	100	2.200	153
Round steak.....	100	3.540	120	Round steak.....	100	3.540	120
Ham.....	25	1.110	62	Orange juice.....	50	0.073	19
Orange juice.....	50	0.073	19	Potato.....	150	0.525	126
Potato.....	100	0.350	84	Dried apple.....	50	0.105	149
Dried apple.....	50	0.105	149	Milk, 1,000 c.c.....	...	5.400	735
Cabbage.....	50	0.161	16	Coffee, c.c.....	175	0.087	...
Squash.....	50	0.112	24	Sugar.....	20	.....	82
Milk, c. c.....	400	2.160	294	Pork fat.....	19	.....	177
Coffee, c.c.....	175	0.087	...				
Sugar.....	20	.....	82				
Pork fat.....	22	.....	205				
Total.....	.....	13.010	2,646	Total.....	.....	16.604	2,971

The total nitrogen and calorie values are based on analyses of the foodstuffs used at the Pellagra Hospital as given by Hunter, Givens and Lewis, and by Sullivan and Jones.<sup>14</sup> The calories for apple and squash are based on Atwater and Bryant's figures.

In general, at entrance to the hospital, the patients were placed on diet G, which contained 13.01 gm. nitrogen representing 81 gm. protein, of which approximately 6.84 gm. nitrogen or 42.8 gm. protein were of

9. Folin: *Am. J. Physiol.* **45**:13, 1905.

10. Steel: *J. Biol. Chem.* **8**:365, 1910.

11. Folin: *Ztschr. f. physiol. Chem.* **41**:223, 1904.

12. Folin-Shaffer: *Ztschr. f. physiol. Chem.* **32**:552, 1901.

13. Folin-Denis: *J. Biol. Chem.* **26**:501, 1916.

14. Bull. 120, II, Hygienic Laboratory, Washington, 1920.

animal origin. Then as the patients' appetite and demand for food became greater, they were placed on diet B containing 16.604 gm. nitrogen or approximately 103.78 gm. protein, of which 67 per cent. were of animal origin. Diet B, containing a higher protein content and a higher caloric value, was the more curative. However, a number of patients kept on diet G recovered from acute pellagra rapidly. In fact, the improvement in well being and the subsidence of pellagra symptoms showed that diet G, providing 2,600 calories and containing 13 gm. nitrogen, of which 6.84 gm. are from animal protein, suffices to eradicate the signs and symptoms which, in the judgment of the medical staff, are characteristic of pellagra.

June 22, 1917, a preliminary study was started on all the patients in the hospital to determine wherein the patients differed from normal people. Lombroso, as quoted by Marie,<sup>15</sup> found that in all his cases the phosphate of the urine was diminished in spite of good nutrition. Camurri likewise found the phosphate of the urine of pellagrins less than that of normal people. Camurri also found that the proportion of urea to total nitrogen was diminished, and that the ratio of ammonia nitrogen to total nitrogen was increased particularly in cases where the diet was predominantly a maize diet. Myers and Fine found that the elimination of total nitrogen, urea, ammonia, uric acid and creatinin is slightly below the normal, though the constituents dependent on exogenous origin, namely, the uric acid and creatinin, are such as might be observed in other persons of similar physical condition. Their data for the percentage of ammonia and undetermined nitrogen are slightly above the so-called normal figures, and the other constituents are slightly below, differences which they interpret as due to the diet and the physical condition of the patients.

In our preliminary work, it was found that the excretion of phosphates by the pellagra patients, even on a very good diet with a high milk content, was less than that of normal people. As the patient improved in general condition, and pellagra symptoms disappeared, the excretion of phosphates in the urine increased. This increase in the excretion of phosphates is tied up undoubtedly with a greater assimilation of food, and, perhaps, though this point was not tested, with an improved functioning of the kidneys. In the preliminary period the excretion of total amino-acid nitrogen as determined by the Van Slyke gasometric method<sup>16</sup> varied from 0.126 to 0.335 gm. amino-nitrogen with an average of 0.211 gm., or 3 per cent., of the total nitrogen for the active cases; from 0.148 to 0.516 gm., with an average of 0.271 gm., for the convalescing and the cases about to be discharged, and

15. Marie: *Pellagra*, Translated by Lavinder and Babcock, Columbia, S. C., 1910.

16. J. Biol. Chem. **16**:125, 1913.

from 0.136 to 0.310 gm. with an average of 0.214 gm. for the four normals.

According to Murlin<sup>17</sup> the absolute amount of mon-amino-acid nitrogen in the urine of normal persons on a mixed diet is from 0.15 to 0.30 gm. per day. This fact, coupled with the results from normal urines here, shows that the total amino-acid nitrogen of the twenty-four hour urine is normal in amount both in active and convalescing cases of pellagra. The latter ran somewhat higher, but the difference is in accord with the high milk diet on which the convalescent patients had been for a longer time for, as shown by Long and Gephart,<sup>18</sup> on a milk diet, the fraction of undetermined nitrogen, which includes the amino-acid nitrogen, is higher than on ordinary mixed diet.

For the patients, in general, but especially for the acute cases recently admitted, the total nitrogen of the preliminary period was low, the excretion of ammonia tended to be increased, and the ratio of ammonia nitrogen to total nitrogen was high. As the patients improved, the ammonia excretion and the ammonia ratio returned to normal and was within normal limits some times before the patients were discharged. The data for phosphates, amino-acids, total nitrogen, and ammonia for the preliminary period are given in Tables 2, 3 and 4. The preliminary study suggested that the study of the nitrogen partition of the urine would be profitable.

TABLE 2.—PHOSPHORIC ACID ( $P_2O_5$ ) CONTENT OF URINE IN GRAMS;  
(A) FIRST TEST; (B) LAST TEST

Case	Date of Admission	Date of Discharge	Status of Pellagra at Time of Testing	Date of Test				
				6/28	7/2	7 5	7/9	7 13
				$P_2O_5$ , Gm.	$P_2O_5$ , Gm.	$P_2O_5$ , Gm.	$P_2O_5$ , Gm.	$P_2O_5$ , Gm.
327	6/13	8/21	Active pellagra	....	(a)0.964	1.648	1.328	(b)1.958
328	6/13	8 17	Active pellagra	(a)0.821	0.802	0.891	1.470	(b)1.929
341	6/24	8 25	Active pellagra	(a)1.734	1.743	....	1.393	(b)1.940
347	6/27	8 9	Active pellagra	....	....	(a)0.900	1.018	(b)1.402
352	7/ 2	7/ 6	Active pellagra	....	....	0.764*	....	....
318	5/12	7/14	Convalescent	....	....	(a)1.285	1.008	(b)1.712
323	5/21	7 16	Convalescent	....	(a)1.376	1.167	1.749	(b)2.567
325	5 26	8/30	Convalescent	....	(a)1.163	1.339	1.331	(b)1.626
328	5/29	8 20	Convalescent	....	....	....	....	2.065
Con- trols								
1	....	....	Nonpellagrous	(a)1.887	1.629	....	....	(b)2.233
2	....	....	Nonpellagrous	(a)2.939	2.149	2.958	1.877	(b)2.159
3	....	....	Nonpellagrous	....	(a)1.565	1.870	1.681	(b)2.348
4	....	....	Nonpellagrous	....	....	....	(a)1.365	(b)1.735
Average first tests active pellagra patients exclusive of case 352.....								1.105
Average last tests active pellagra patients exclusive of case 352.....								1.805
Average first tests convalescent patients exclusive of case 328.....								1.275
Average last tests convalescent patients exclusive of case 328.....								1.908
Average first tests controls.....								1.939
Average last tests controls.....								2.119

\* Left hospital unimproved.

17. Murlin: Bull. 116, III, Hygienic Laboratory United States Public Health Service, 1920.

18. Long and Gephart: J. Am. Chem. Soc. **34**:1229, 1912.

TABLE 3.—AMINO-ACID NITROGEN CONTENT OF THE URINE

Case	Date of Admission	Status of Pellagra at Time of Testing	Date of Tests					
			6/23	6.28	7/2	7/5	7.9	7/13
			Amino Acid N, Gm.	Amino Acid N, Gm.	Amino Acid N, Gm.	Amino Acid N, Gm.	Amino Acid N, Gm.	Amino Acid N, Gm.
323	6/6	Active pellagra	0.195					
337	6/13	Active pellagra	.....	0.252	.....	0.225	0.273	0.335
338	6/13	Active pellagra	0.214	0.235	.....	0.219	0.179	0.161
339	6/15	Active pellagra	0.136					
341	6/24	Active pellagra	.....	0.169	.....	0.162	0.268	0.107
347	6/27	Active pellagra	.....	.....	.....	0.185	0.237	0.227
352	7/2	Active pellagra	.....	.....	.....	0.225		
318	5/12	Convalescent	.....	0.295	.....	0.286	0.180	0.325
319	5/12	Convalescent	0.305	0.283				
323	5/21	Convalescent	.....	9.234	0.148	0.345	0.492	0.195
324	5/24	Convalescent	.....	0.516				
325	5/26	Convalescent	.....	0.263	0.222	0.287	0.228	0.201
328	5/29	Convalescent	.....	.....		.....		0.181
332	6/4	Convalescent	0.229					
Controls								
1	.....	Nonpellagrous	.....	0.136	0.248	.....	.....	0.218
2	.....	Nonpellagrous	.....	0.202	.....	0.237	0.263	0.286
3	.....	Nonpellagrous	.....	0.151	.....	0.310	0.179	0.163
4	.....	Nonpellagrous	.....	.....	.....	.....	0.170	
Average of tests of pellagra patients.....								0.211
Average of tests of convalescent patients.....								0.271
Average of tests of controls.....								0.214

TABLE 4.—PRELIMINARY PERIOD. TOTAL NITROGEN, AMMONIA NITROGEN, AND AMMONIA N RATIO TO TOTAL NITROGEN

Case	Date Admitted	Total Nitrogen, Gm.				Ammonia Nitrogen, Gm.				Ammonia N to Total Nitrogen, per Cent.			
		6/23	6.28	7/5	7/9	6/22	6.27	7/5	7/9	6/22	6.27	7/5	7/9
Active													
331	6/4	9.62	.....	.....	.....	0.684	.....	.....	.....	7.58			
333	6/6	7.448	.....	.....	.....	1.502	.....	.....	.....	20.17			
337	6/13	8.439	7.310	10.575	9.780	1.497	1.399	1.619	1.126	17.74	19.14	15.31	11.51
338	6/13	4.782	6.431	6.481	8.395	0.987	1.243	1.069	1.091	20.64	19.33	16.96	13.00
339	6/15	8.439	.....	.....	.....	0.507	.....	.....	.....	6.01			
341	6/24	.....	5.936	3.955	5.479	.....	0.724	0.765	0.593	.....	12.20	17.83	10.82
347	6/27	.....	.....	5.590	6.890	.....	.....	0.409	0.328	.....	.....	7.14	4.76
352	7/2	.....	.....	7.420	.....	.....	.....	0.595	.....	.....	.....	8.02	
Average....		7.626	6.559	6.864	7.636	1.035	1.122	0.885	0.785	14.43	16.89	13.05	10.02
Convalescing													
312	5/1	12.527	.....	.....	.....	0.736	.....	.....	.....	5.88			
318	5/12	8.859	8.727	10.805	15.730	0.477	0.578	0.927	0.824	5.38	6.62	8.58	5.24
319	5/12	13.940	15.752	.....	.....	0.800	0.968	.....	.....	6.28	6.34		
323	5/21	13.026	11.146	9.499	12.044	0.927	0.854	0.995	0.913	7.12	7.66	10.47	7.58
324	5/24	8.180	8.932	.....	.....	1.390	0.911	.....	.....	17.00	10.26		
325	5/26	10.881	6.185	10.410	10.358	1.374	1.170	0.882	0.610	12.63	18.50	8.47	6.01
327	5/27	7.448	.....	.....	.....	0.492	.....	.....	.....	9.29			
330	6/2	9.619	.....	.....	.....	1.137	.....	.....	.....	11.72			
332	6/4	9.839	.....	.....	.....	0.839	.....	.....	.....	8.53			
Average....		10.489	10.148	10.228	12.644	0.940	0.902	0.925	0.782	9.33	9.94	9.17	6.28
Controls Nonpellagrous													
1	.....	11.262	10.905	.....	.....	0.690	0.572	.....	.....	5.33	5.68		
2	.....	14.962	15.170	15.890	12.916	0.938	0.783	0.889	0.888	6.43	5.18	5.66	6.35
3	.....	13.880	9.032	15.060	10.566	0.575	0.348	0.741	0.490	4.14	3.84	4.92	4.64
4	.....	9.162	8.856	.....	7.072	0.431	0.445	.....	0.379	4.70	5.02	.....	5.36
Average....		12.302	10.773	15.475	10.195	0.641	0.537	0.820	0.564	5.15	4.93	5.29	5.45





From July 13 to Sept. 13, 1917, inclusive, the urine was analyzed for each patient at entrance or shortly after entrance to the hospital and then at least twice a week. From Sept. 13, to Oct. 11, 1917, the urine was analyzed only once a week. The analyses included the determination of volume, specific gravity, total nitrogen, urea, ammonia, uric acid and creatinin, and the qualitative testing for indican and albumin of the twenty-four hour urine for all uncomplicated or little complicated cases in the hospital. The collected data are given in Table 5 with the cases arranged in groups according to the severity of the symptoms. The different items of the table may be dealt with separately at least in part.

#### VOLUME AND SPECIFIC GRAVITY

The average volume individually for the four normal individuals in fifty-seven tests from July 13 to October 11 was 1,176, 1,009, 759, 855 c.c., respectively, with a general average of 950 c.c. The corresponding specific gravities were 1.027, 1.032, 1.031, and 1.031, respectively, with a general average of 1.030. These data were gathered in warm weather, when the controls were perspiring freely in the warm laboratory. The average for the first two tests in July for the controls was 936 c.c. volume and 1.031 specific gravity. The average volume for the last tests for four normal persons working in the laboratory from August 22 to August 31 was 844 c.c. The averages for the first estimation of volume and specific gravity for twenty-six pellagra patients, when the patients were nearest the active pellagra period and the shortest time on a remedial diet, were 1,158 c.c. and 1.0196 respectively. These averages include a case of polyuria. Excluding this case, the average volume for the pellagra patients becomes 1.039 c.c., and the average specific gravity 1.020.

The average of the last determinations for the patients taken just before each patient was discharged or for a few patients a short time before discharge, at the time the patient was well on the road to convalescence and showed no outward sign of pellagra, was 1,420 c.c. for volume and 1.0196 for specific gravity. Excluding the case of polyuria of over 3,800 c.c. volume, the volume of the urine in the last determinations becomes 1,322 c.c. and the specific gravity 1.020.

Excluding the case with polyuria, nineteen out of twenty-five cases increased in volume of the urine in the hospital; seventeen increased in specific gravity; seven increased in both volume and specific gravity; two increased in specific gravity with little change in volume; and one increased considerably in volume with no change in specific gravity.

Of the cases studied, three classifications were made: those with intense extensive eruption or with considerable erythema and marked general malnutrition and general weakness were classed as severe cases;

those with considerable erythema and with but slight evidence of malnutrition and weakness were classed as moderate cases; those with mild skin symptoms and slight systemic involvement were classed as mild cases.

Excluding the case of polyuria in the estimation of volume, the severe cases have a much smaller volume (799 c.c.) than the moderate cases (1,053 c.c.) and these, in turn, less than the mild cases (1,376 c.c.).

The possibility that the increase in average volume of urine from the active pellagrous stage to the stage in which the signs and symptoms of pellagra have disappeared is tied up with a change in season or a temperature change with less sweating, is but a small part—a very small part—of the explanation of the change in volume. Thus, of seven cases (Cases 353, 357, 337, 347, 358, 378, 375) in the tests from July 12 to August 31, the increase in average volume from the first test to the last is from 831 c.c. to 1,374 c.c. Four normal persons, working in the laboratory, varied in that period from 936 average volume to 844 c.c.—a slight loss in fact. Five cases (Cases 341, 381, 285a, 370, 390, for the most part cases with large initial volume) decreased in volume from the first test to the last tests, during the period from July 12 to October 11. Several cases (Cases 400, 385, 395) were practically constant in volume in the first and last tests. For Case 338, the cessation of the diarrhea would explain in part, at least, the increase in volume in the convalescent stage. The change in volume between the first and last tests in the hospital would thus seem to be tied up with a greater or less return of the patients to the average volume that would normally obtain for them on a diet such as they had at the hospital and a similar mode of living. This conclusion is strengthened by the fact that the average for all types of cases, severe, moderate and mild in the last analyses is approximately 1,400 c.c.

The increased volume of the urine of the convalescent cases in the hospital may be due: (1) to a change in the consistency of the feces (what few batches of feces we had occasion to examine were, in the active stage of the disease, rather bulky and soft with apparently a high water content); (2) to greater intake of food with a resultant greater intake of fluid, and (3) to the greater intake of water as such to aid in the excretion of the greater nitrogenous waste as found in the urine in the convalescent stage. As to the volume of the urine in pellagra, Marie<sup>19</sup> states: "Of 100 pellagra patients, the quantity of urine in twenty-four hours showed an average of 900 c.c. with a minimum of 500 c.c., and a maximum of 1,900 c.c. The quantity is, therefore, less

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19. Marie: Pellagra. Translated by Lavinder and Babcock. Columbia, S. C., 1910, p. 215.

than normal. Calderni also found in 35 per cent. of his pellagra patients a great diminution of the quantity of urine."

Whatever may be the reason, therefore, the fact remains that for the pellagrins studied at the pellagra hospital in 1917 there is predominantly a decrease in the volume of the twenty-four hour urine in the pellagrous period as compared with the stage when the signs and symptoms have disappeared.

#### TOTAL NITROGEN

The elimination of total nitrogen, as shown by the tests made as soon as possible after the patient had been admitted to the hospital, was very much below that of normal persons.

The total nitrogen of the urine of twenty-six cases (Cases 337 to 400) in the first tests made, including analyses made in one case (Case 371) of the twenty-four hour urine collected in the home one week before admission to the hospital varied from 3.043 to 10.468 gm., with an average of 6.214 gm. The total nitrogen of the urine in the first test after admission to the hospital with at least one day on the hospital diet varied from 3.043 to 10.468 gm., with an average of 6.257 gm. When divided according to the severity of symptoms, the average total nitrogen of ten severe cases at the first test made on or very shortly after entrance to the hospital was 4.857 gm.; of ten moderate cases 6.695 gm.; and of 6 mild cases 7.669 gm. The total nitrogen for the last estimation before discharge varied from 5.199 in Case 353 (with some mental symptoms and a finicky appetite) to 15.398 gm., with an average of 10.588 gm. Leaving out this case in the last estimation, the average total nitrogen of the urine of the cured patients becomes 10.804 gm. Here, again, the total nitrogen of the urine of 10 severe cases (9.848 gm.) is lower than that of the moderate cases (10.642 gm.) and the mild cases (11.733 gm.).

#### AMMONIA, UREA, URIC ACID, CREATININ

Total nitrogen of the urine collected shortly after the patient had entered the hospital is on the average, as shown, low (6.214 gm.). The urine likewise shows a low absolute content of ammonia nitrogen (0.519 gm.); a low uric acid (0.116 gm.); a low creatinin nitrogen (0.279 gm.); a low urea nitrogen (4.457 gm.). The ratio of urea nitrogen to total nitrogen is low (71.81); the ammonia ratio is high (8.453); the creatinin ratio slightly high (4.60); the undetermined nitrogen ratio high (13.48); the creatinin coefficient low (5.82). The low ratio of urea nitrogen to total nitrogen and the heightened ammonia ratio are in accord with the findings of Camurri, while the data, as a whole, are an accentuation of the findings of Myers and Fine.

In the case of the urine of the same patient about to be discharged, or well along in the convalescent stage with no outward manifestation of pellagra and with a heightened joy of living and sense of well being, the total nitrogen and urea are much increased; the urea ratio is much greater; the ammonia ratio is much reduced; and the ratio of undetermined nitrogen is much reduced.

When the patients are divided into groups according to the severity of the symptoms, extent and vividness of the erythema and general weakness and malnutrition with more or less skin symptoms, it may be seen from Table 5 that the severe cases have a smaller value for volume (excluding a case of polyuria) specific gravity, total nitrogen, ammonia nitrogen, uric acid nitrogen and urea, and for the creatinin coefficient than the moderate cases and the moderate cases less than the mild cases. On the other hand, the severe cases have a higher ratio of ammonia nitrogen to total nitrogen than the moderate cases and these, in turn, have a higher ratio than the mild cases.

Bearing in mind the results of the urinary analyses made shortly after the patient had entered the hospital, it becomes of interest to compare the results of Table 5 (a) with the data given by Folin on different diets of low and high protein.

Folin<sup>20</sup> shows that urine obtained from normal persons does not necessarily exhibit any such constancy in composition as has been supposed to be the case. Quantitative changes in the daily protein catabolism are accompanied by pronounced changes in the distribution of the urinary nitrogen and sulphur and the variations occur according to laws that can be formulated with a fair degree of precision. The nature of these variations may be expressed by the following generalizations.

"1. *Creatinin*.—The absolute quantity eliminated in urine on a meat-free diet is a constant quantity different for different individuals but wholly independent of quantitative changes in the total amount of nitrogen eliminated.

"2. *Uric Acid*.—When the total amount of protein metabolism is greatly reduced the absolute quantity of uric acid is diminished but not nearly in proportion to the diminution in the total nitrogen and the per cent. of uric acid in terms of the total is therefore much increased.

"3. *Ammonia*.—With pronounced diminution in the protein metabolism as shown by the total nitrogen in the urine there is usually but not always and therefore not necessarily a decrease in the absolute quantity of ammonia eliminated. A pronounced reduction of the total nitrogen is, however, always accompanied by a relative increase in the

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20. Folin: Laws Governing the Chemical Composition of Urine, *Am. J. Physiol.* **13**:67, 1905.

ammonia nitrogen, provided that the food is not such as to yield an alkaline ash.

"4. *Urea*.—With every decided diminution in the quantity of total nitrogen eliminated there is a pronounced reduction in the per cent. of that nitrogen represented by urea. When the daily nitrogen has been reduced to about 3 or 4 gm., about 60 per cent. of it only is in the form of urea."

The picture afforded by the results of urinary analysis in the active pellagra stage of the hospital patients of 1917 is that of malnutrition and low protein metabolism with low total nitrogen elimination; with, in general, a lowered ammonia elimination, though a few have an absolute increase in ammonia elimination; with, in general, a heightened ratio of ammonia nitrogen to total nitrogen; with the uric acid somewhat diminished but not in proportion to the total nitrogen; with a low creatinin but with little variation with change in the total nitrogen from the pellagrous to the convalescent stage; with low urea and a low ratio of urea nitrogen to total nitrogen. It may be pointed out that the urea ratio in some cases with not very low total nitrogen (Cases 337, 338, 369 and 375), is much lower than would be expected. Thus, the average total nitrogen of these four cases is 9.238 gm., the average urea ratio only 64.13.

The constituents dependent on exogenous factors, urea and ammonia, are in agreement with the protein catabolism, those of endogenous origin, uric acid and creatinin, are, in general, in harmony with the poor physical condition of the patients, low vitality and more or less atrophy of muscle.

The uric acid elimination, on the average, differs very little in the active stage from that of the convalescent patients. The creatinin elimination remains low, as shown by the creatinin coefficient, which averages 5.17 for the acute stage of the severe cases and 5.54 for the same patients about to be discharged; 5.52 for the moderate cases and 6.65 for the same patients about to be discharged; 7.39 and 7.15 for the corresponding periods in the case of the mild attacks. The creatinin coefficient of the patients with a mild attack of pellagra is comparable with that of normal persons, which varies from 7 to 11.

The severity of attacks of pellagra may be differentiated primarily by the extent and intensity of the eruption and secondly by the eruption, general malnutrition, and subjective symptoms. Goldberger, Wheeler, and Sydenstricker<sup>21</sup> suggest "the possibility if not the probability that pellagra includes at least two commonly associated but etiologically essentially distinct though closely related syndromes, namely: (1) the

21. Goldberger, Wheeler and Sydenstricker: J. A. M. A. **71**:944 (Sept. 21) 1918.

syndrome that is comprehended by the phrase "pellagra sine pellagra," and (2) "the dermatitis or pellegra without or with only slight subjective manifestation." Of the hospital patients considered in the present report, at least two rough classifications can be made, (1) those with marked skin symptoms but otherwise not much physical deterioration, a class which may be called dermal; (2) those with moderate or slight skin symptoms but with general weakness, paresthesia, and marked intestinal upset, a class which may be called systemic. The differentiation into classes is more noticeable in the severe cases.

Dividing the severe cases into these groups as shown in Table 6, it may be seen that the total nitrogen, urea nitrogen and creatinin nitrogen of the systemic group are lower than those of the dermal group, and that the ratio of the urea nitrogen to total nitrogen is lower for the systemic group, that the creatinin coefficient is lower, the undetermined nitrogen and the ratio of undetermined nitrogen to total nitrogen is higher. The biochemical study, therefore, offers support for the view of Goldberger, Wheeler, and Sydenstricker as to distinct syndromes.

TABLE 6.—URINARY DATA IN PELLAGRA IN RELATION TO DOMINANCE OF MANIFESTATIONS

Mani- festations Dominant	Total Nitro- gen	Urea Nitro- gen	NH <sub>3</sub> N N	Creat- inin N	Unde- ter- mined N	Ratio Urea N Total N	Ratio NH <sub>3</sub> N Total N	Unde- ter- mined N Total N	Creat- inin Coeff- icient	Casts and Albumin
Dermal:										
Case 341.....	6.576	4.681	0.758	0.186	0.949	71.18	11.53	14.43	4.17	Negative
Case 357.....	5.845	4.387	0.403	0.277	0.671	75.06	6.90	11.47	7.10	Negative
Case 372.....	5.033	4.169	0.344	0.392	0.660	82.83	6.83	6.00	6.24	Negative
Case 384.....	5.568	4.290	0.372	0.232	0.609	77.19	6.69	16.96	5.67	Granular casts
Average....	5.753	4.382	0.469	0.272	0.557	76.57	7.99	10.72	5.80	
Systemic:										
Case 353.....	4.026	2.889	0.357	0.176	0.543	71.76	8.87	13.48	4.06	Albumin
Case 371.....	3.918	2.843	0.236	0.201	0.554	72.56	6.02	14.14	5.08	Hyaline casts
Case 379.....	3.043	1.805	0.417	0.229	0.455	59.32	15.70	14.93	5.26	Albumin
Case 381.....	5.221	3.893	0.394	0.140	0.695	74.56	7.55	13.31	2.87	Negative
Case 386.....	4.880	3.340	0.818	0.246	0.424	68.44	16.76	8.69	5.89	Granular and hyaline casts
Case 400.....	4.466	2.880	0.308	0.169	1.003	64.49	6.90	22.45	5.39	Trace sugar
Average....	4.259	2.942	0.422	0.194	0.612	68.52	9.97	14.50	4.76	

#### FOOD UTILIZATION IN PELLAGRA

The data gathered in Table 5 (a) show the picture of a low protein metabolism. This conclusion brings up the question of food utilization in pellagra, especially the utilization of protein. Including the preliminary period, June 22 to July 13, the total nitrogen of the food consumed during the time the first twenty-four hour urine was being collected varied (as given in Table 7) from 7.134 to 16.571 gm. with an average of 11.388 gm. One week later, the average quantity of food consumed by each individual for the day the urine was being collected and the day

previous, varied from 7.775 to 16.594 gm. with a general average of 12.748 gm. The body weight at the outset of the urine study varied from 39 kg. for an adult female to 68.745 kg. for a strongly built male, with an average of 47.51 kg. The appetite of the patients who had just entered the hospital was, in general, fair, the quantity of food eaten and the nitrogen thereof was not excessively low. However, the nitrogen excreted in the urine, with little gain in weight, remained low for several weeks, as shown in Table 7. It is not uncommon, in fact, to find a slight loss or no gain in weight during the first week or two of residence in the hospital. It would seem that the ability to assimilate food is low in pellagra, that the power to utilize food is in general only slowly regained.

Myers and Fine,<sup>4</sup> working in cooperation with the Thompson-McFadden Commission, conclude from their results on metabolism studies of pellagrins that the ability of the pellagrins to absorb their food is only slightly, if at all, impaired, and that whatever impairment there was is, in part, due to diarrhea. Myers and Fine's cases, as judged by their case histories, were for the most part mild cases at the time experimental work began.

Hunter, Givens and Lewis<sup>5</sup> studied nitrogen balances on seven patients at the Pellagra Hospital, Spartanburg, S. C., in 1914. Two of these patients (Cases 2 and 14) had been on a highly nourishing remedial diet for twenty-six and eighteen days, respectively, before the metabolism study was started. One of these at entrance was a mild case, the other was a severe case. The utilization of protein by these cases was, respectively, practically 93 and 88 per cent. The five other cases studied by Hunter, Given and Lewis for nitrogen balances (Experiments 3 to 7, Cases 1, 19, 36, 46 and 32) were on a low protein vegetable diet, somewhat comparable to a pellagra producing diet. These five cases showed a low protein utilization. Thus, Case 1 showed a protein utilization varying from 76 to 85; Case 19, from 60 to 67 per cent.; Case 36 over the whole period of twenty-three days had a protein utilization of only 71.5 and for the first period of eight days, the period of best utilization, only 77.2 per cent.; Case 46 over the whole period of study of twenty-seven days had a protein utilization of 81.5 per cent.; Case 32, described as a mild case, was for seven days on the vegetable diet, for a second period of nine days on a modified vegetable diet, and for seven days on a diet containing a high content of animal protein in the form of meat and eggs. During the first two periods, the nitrogen balances were negative and the protein utilization was low, 73.5 per cent.; during the last period on a high protein diet the utilization was 87.5 per cent.

It would seem, therefore, that on a low protein vegetable diet the utilization of protein by active pellagrins is low and that, as shown in

TABLE 7.—DATA ON RELATION OF NITROGEN INTAKE AND EXCRETION TO WEIGHT

Case	Date of First Analysis in Hospital	Nitrogen of the Urine, Gm.			Nitrogen of the Food Eaten, Gm.			Body Weight, Kg.					Nitrogen of Urine and of Food and Body Weight at End of Experiment			Date of Last Urine Tests	Last Weight in Hospital	
		First Analysis	Second Analysis, 1 Week Later	Third Analysis, 2 Weeks Later	First Analysis	Second Analysis	Third Analysis	First Anal-ysis	Second Anal-ysis	Third Anal-ysis	Urine,* Gm.	Food, Gm.	Body Weight, Kg.	Date of Last Urine Tests	Weight, Gm.		Date of Last Weighing	
337	6/23/17	8.44	7.210	9.790	11.895	14.535	16.590	68.745	69.850	69.650	16.398	19.022	72.35	8/21	72.35	8/18/17		
338	6/23/17	4.782	7.002	8.395	7.735	12.979	13.633	39.55	40.154	38.700	12.808	16.625	40.15	8/16	40.15	8/11/17		
341	6/28/17	5.936	5.479	6.576	8.582	14.751	16.004	44.134	43.150	41.650	13.655	16.604	47.35	8/22	47.19	8/25/17		
347	7/7/17	5.590	7.173	7.947	8.291	11.062	11.291	39.944	40.550	41.035	8.856	12.108	41.66	8/7	41.65	8/4/17		
353	7/30/17	4.130	4.026	2.924	7.134	10.775	9.273	34.535	35.300	42.790	5.199	9.708	41.65	8/16	41.35	8/18/17		
357	7/17/17	6.845	6.130	7.130	7.130	10.775	10.775	39.944	40.035	40.350	10.064	16.679	42.16	8/16	44.35	9/1/17		
358	7/17/17	9.602	7.027	7.130	8.693	12.979	13.633	43.743	43.58	43.150	9.278	12.948	45.06	8/31	44.46	9/1/17		
360	8/4/17	9.154	7.321	9.410	13.179	16.594	16.590	51.75	52.750	53.150	9.890	12.958	54.15	9/13	53.15	9/29/17		
370	8/7/17	8.151	7.321	9.410	13.179	16.594	16.590	51.945	50.250	49.950	9.758	16.580	54.445	9/27	54.445	9/29/17		
371	8/10/17	5.930	9.450	10.885	8.671	10.890	14.813	39.55	40.250	39.550	11.994	15.236	45.15	10/11	55.35	4/6/18		
372	8/9/17	5.933	13.785	11.313	16.517	16.580	16.571	62.881	63.250	63.950	14.779	19.763	69.75	10/11	79.601	4/13/18		
375	8/11/17	8.499	11.860	14.578	13.063	12.936	16.661	56.350	55.550	55.750	13.572	16.580	56.75	8/31	59.65	10/13/17		
378†	8/14/17	3.043	8.190	.....	11.144	10.454	.....	47.545	48.350	.....	9.031	12.565	48.35	8/22	49.15	8/25/17		
379	8/16/17	4.240	0.474	8.163	12.119	11.989	12.955	43.55	44.450	44.550	11.751	12.967	46.75	9/27	46.75	9/29/17		
381†	8/21/17	5.221	8.732	.....	12.957	11.924	.....	48.780	49.150	.....	8.732	11.924	49.15	8/31	49.15	9/1/17		
384	8/29/17	3.065	5.538	9.115	9.792	11.413	14.702	41.355	40.950	42.350	11.653	16.069	46.15	10/11	46.15	10/13/17		
385	8/28/17	6.002	10.630	9.229	11.874	15.004	14.430	39.145	39.650	39.950	9.226	14.430	39.95	9/13	39.95	9/15/17		
389†	8/28/17	4.890	10.298	.....	14.599	10.548	.....	41.780	41.150	.....	10.228	16.390	41.15	9/6	41.15	9/8/17		
387	8/28/17	7.004	8.598	.....	13.062	12.949	.....	50.575	49.750	50.350	16.484	13.846	52.35	10/11	52.35	10/13/17		
388	8/29/17	6.049	8.074	7.859	8.463	12.951	12.951	62.250	51.750	52.150	8.171	12.952	52.55	9/29	52.55	9/22/17		
389	8/29/17	4.354	8.487	9.089	12.944	12.951	12.952	51.050	49.950	50.150	14.068	16.541	53.15	10/11	53.15	10/13/17		
390	9/1/17	7.950	8.638	10.075	12.740	12.967	16.328	53.2	53.350	52.550	12.963	15.046	53.35	10/4	53.35	9/29/17		
393	9/7/17	7.965	8.818	12.053	14.087	14.150	13.871	49.545	49.250	49.550	14.395	16.540	50.85	10/11	51.35	12/15/17		
395	9/11/17	5.132	8.140	10.263	14.087	14.150	13.871	47.480	45.750	46.845	9.244	16.346	46.75	10/4	46.55	11/30/17		
396	9/12/17	5.889	8.553	11.464	12.632	12.952	13.947	55.540	55.250	55.150	16.131	13.610	57.05	10/4	57.05	10/6/17		
400	9/23/17	4.466	6.391	5.662	10.110	10.672	14.669	31.350	32.550	32.550	4.883	16.390	33.35	10/11	34.75	11/10/17		
Average.....		5.923	8.135	9.132	11.388	12.748	14.176	47.569	47.394	47.502	10.755	14.805	49.453	.....	50.727			

\* The nitrogen of the urine and of the food, and the body weight is not necessarily the same as given in the last test of Table 5 since the complete analysis of the urine of Table 5 stopped in some instances before the last analysis of the urine for total nitrogen.

† Left the hospital after little improvement contrary to advice. Excluding these cases (378, 381, 382) the average weight at entrance becomes 47.702 kg., at discharge 51.281 kg.



Case 32 of Hunter, Givens and Lewis' study, the utilization of the protein of a high animal protein diet was 87.5 per cent. when determined immediately after the change from low protein to a high protein diet.

Wilson and Roaf<sup>22</sup> carried out a partial metabolism experiment on two groups of men in Egypt; a group of five healthy men and a similar group of five pellagrins said to be in the convalescent stage. They found the loss of nitrogen in the feces was "35 per cent. in the pellagrins, and 33 per cent. in the healthy men, a difference of 6 per cent."

In our work it was found that with no gain in weight on the average, with a good intake of nitrogen, the nitrogen of the urine in the early days of the patient's stay in the hospital was small. These findings implied that the utilization of protein was low. Accordingly, a group of patients was selected for a study of the nitrogen balance for a three-day period, July 31 to August 2, inclusive. The results are given in Table 8. The protein utilization varied from 73.9 per cent. for a severe case, a patient who had been on hospital diet G for fifteen days, to 92.6 for a severe case in which hospital diet B was given for thirty-seven days, with an average for the six patients of 84.5. It is now our belief that we worked with patients well on the way to convalescence, and that if we had tested patients in the first few days of their residence in the hospital, the protein utilization would have been smaller. In passing, it might be said that in three or four weeks on a diet rich in milk, meat, and eggs, etc., the patients greatly improve in well being, in the joy of living, and that in addition the skin symptoms show marked amelioration.

TABLE 8.—PROTEIN UTILIZATION IN PELLAGRA

Case	Nitrogen of Food	Nitrogen of Urine	Nitrogen of Feces*	Nitrogen of Urine and Fecal Nitrogen	Nitrogen Balance	Per-centage Utiliza-tion of Protein	Diet	Days on Diet Before Utiliza-tion Test	Diarrhea
337	19.197	13.486	3.513	16.999	2.198	81.7	B+½	48	No
338	16.604	10.930	1.505	12.455	4.169	90.9	B	48	No
341	16.604	8.458	1.236	9.694	6.910	92.6	B	31	No
347	12.311	9.444	1.848	11.292	1.019	85.0	G	34	No
367	12.922	8.727	3.391	12.118	0.874	73.9	G	15	No
368	12.812	7.711	2.233	9.944	2.868	82.6	G	15	Slight
Aver.	15.087	9.793	2.288	12.081	3.006	84.5	..	32	

\* Carmin was used as a marker. The nitrogen was determined on the fresh sample.

The facts on protein utilization as marshalled by us are: (1) patients who had been on a remedial diet for at least fifteen days before the protein utilization tests were made showed a utilization varying from 73.9 to 92.6 per cent., with an average of 84.5 per cent.; (2) in the

22. Wilson and Roaf: Report of a Committee Regarding Prevalence of Pellagra Among Turkish Prisoners of War, 1919. Appendix 8, p. 57.

first analysis after entrance to the hospital and one week later the average nitrogen of the urine was only 5.923 and 8.135 gm., respectively, while the average nitrogen of the food eaten was 11.388 and 12.748 gm., respectively; (3) that notwithstanding a good intake of food, there was no gain in weight in the first week in the hospital. Taking all these data together, we should judge that the utilization of protein by persons suffering with marked pellagra tends to be somewhat subnormal.<sup>23</sup>

#### QUALITATIVE TESTS

*Indican.*—Indican<sup>24</sup> as determined by Obermayer's reagent and extraction with chloroform was positive in the urine of all patients. The occurrence of indican in the urine has been reported by a number of investigators. In our work, the indican reaction was much stronger for the severe cases than for the moderate or mild cases. No great stress was put on indican in the urine as a symptomatic mark in pellagra, however, for as well shown by Hunter, Givens and Lewis, pellagra is compatible with any degree whatever of indican production even with none at all and Goldberger and Wheeler found little, if any, indican in the urine of their volunteers on a mainly cereal diet by means of which they experimentally produced pellagra in previously healthy normal persons. Further, following the lead of Myers and Fine who found increased amounts of indol and skatol in the feces of pellagrins, several cases were noted in which the feces would give strong qualitative tests for indol and skatol with little indican in the urine. Baumstark<sup>25</sup> claims that *indol formation in the intestine and the excretion of indoxyl do not run parallel*.

All the patients tested showed indican in the urine, some strikingly. The indican must arise from more or less putrefaction in the intestine due to a varying degree of nonutilization of protein, to slow assimilation of protein fission products such as tryptophan, to a varying degree of retention of feces, and an active putrefactive flora.

*Unknown Substances.*—Ehrlich's diazo reaction<sup>26</sup> and Russo's methylene blue reaction<sup>26</sup> were positive in the urines of many of the hospital patients.

23. Some investigators of pellagra believed that once a pellagrin always a pellagrin. This view is no longer tenable. Despite the fact that in many cases the gastric juice is more or less deficient in hydrochloric acid even in the cases as discharged from the hospital, the general condition, activity, and appearance of the discharged patients as a whole would put them in the normal class, a class they would remain in as far as pellagra is concerned as long as the proper diet and normal modes of living are adhered to.

24. Most of the indican tests were made by Assistant Surgeon C. H. Waring of the medical staff.

25. Baumstark: München, med. Wehnschr. 1:722, 1903.

26. See Hawk's Practical Physiological Chemistry, Ed. 5, Philadelphia, P. Blakiston Sons Co., pp. 454, 455, 1917.

*Physiologic Bases.*—Taking the high indican and the diazo reaction of the urine, and the presence of skatol and indol in the feces, as suggestive of an abnormal protein metabolism, large batches of the patients' urine were tested for physiologic bases. The bases sought for were beta-iminazolyl-ethylamine ( $C_5H_9N_3$ ) which Ackermann<sup>27</sup> found to be produced from histidin by the action of putrefactive bacteria and obtained from the intestinal mucosa by Barger and Dale<sup>28</sup>; indolethylamin ( $C_{10}H_{12}N_2$ ) obtained by Ewins and Laidlaw<sup>29</sup>; parahydroxyphenyl-ethylamine from tyrosin as shown by Barger and Walpole<sup>30</sup>; the diamins, putrescin and cadaverin. Using accepted methods, various types of basic material were isolated from the pellagrous urines but not in large enough amounts to be satisfactorily identified.

*Albumin and Casts.*—Evidence of kidney abnormalities in pellagra has been previously reported.<sup>31</sup> In the Illinois investigation, degenerative changes were found in the renal epithelium with more or less interstitial nephritis. Myers and Fine found granular and hyalin casts in the urine of a number of cases. In our work little evidence of kidney change was noted for the mild cases. Of the severe and moderate cases, about 50 per cent. gave evidence of kidney abnormalities as witnessed by the presence of albumin and casts in the urine.<sup>32</sup> However, as shown in Table 5, there can be marked cases of pellagra with no evidence whatever of kidney change.

#### SUMMARY

The study of the urine in pellagra at the U. S. Pellagra Hospital in 1917 may be summarized as follows:

1. The mineral metabolism seemed to be abnormal especially in the actively pellagrous stage as witnessed by the low  $P_2O_5$  excretion despite the fact that the diet taken at the time was a generous one with abundance of milk.
2. Indications were present of a heightened putrefactive process in the intestines.
3. The presence of casts or albumin or both casts and albumin in the urine gave evidence of more or less kidney change in about 50 per cent. of the cases. Marked pellagra can occur with no evidence of kidney change.

27. Ackermann: Ztschr. f. physiol. Chem. **64**:504, 1910.

28. Barger and Dale: J. Physiol. **41**:499, 1911.

29. Ewins and Laidlaw: Proc. Chem. Soc. **26**:343, 1910.

30. Barger and Walpole: J. Physiol. **38**:343, 1909.

31. Pellagra in Illinois. Condensed Report of the Illinois Pellagra Commission, Arch. Int. Med. **10**:123, 219 (July-Aug.) 1912.

32. The evidence regarding casts in the urine was taken from the clinical records made by Assistant Surgeon C. H. Waring.

4. There was low excretion of total nitrogen and the ordinary urinary ingredients.

5. The urea ratio, in general, was low, and in certain cases with fair total nitrogen the urea ratio was lower than should be expected—a finding which suggests liver insufficiency.

6. There was a heightened ratio for ammonia nitrogen and undetermined nitrogen.

7. The metabolic level during the active stage of the disease was low as further shown by the low excretion of uric acid and creatinin.

8. The creatinin coefficient was much below normal.

9. The utilization of protein was found to be subnormal, even after several weeks of a remedial diet.

10. With at least a month on the curative diet, the urinary ingredients rose to approximately normal amounts, the urea ratio rose to normal and the ammonia ratio fell to normal.

11. As suggested by Goldberger, Wheeler and Sydenstricker, the disease may be differentiated into at least two types: (1) a type with marked skin symptoms but with little physical degeneration; and (2) a type with slight skin symptoms but with profound systemic involvement. The abnormality in the urinary findings was greater for the systemic type than for the dermal type.

## HEMOCHROMATOSIS

### REPORT OF FOUR CASES \*

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Hemochromatosis is a chronic disease of males occurring during middle life. Abbott<sup>1</sup> has reported one authentic case in a woman. It is characterized by (1) a pigmentation of the skin that varies from yellow to ashen gray and involves by preference the exposed parts, the axillae, and the genitals; (2) cirrhosis of the liver with moderate enlargement; (3) slight enlargement of the spleen; (4) fibrosis of the pancreas and lymph nodes; (5) hyperglycemia with or without glycosuria.

It is not a common disease. There are records of but four cases of genuine hemochromatosis among 5,000 recent necropsies in Bellevue Hospital. Fuchter<sup>2</sup> found only three instances of this disease in the clinical records of the Johns Hopkins Hospital, covering 106,000 admissions.

Clinically, hemochromatosis may easily be confused with other diseases attended by pigmentation of the skin. The pigment may not be visible. It may be late in its occurrence. It is very frequently a postmortem revelation. During life the only certain method of diagnosis is the microscopic demonstration of iron reacting pigment in the skin.

*Pathogenesis of the Disease.*—The chief interest in this disease centers around the remarkable and widespread pigmentation that occurs. In fact, if we could lose sight of the presence of this pigment altogether, the pathology of the disease would narrow itself down to that of an ordinary cirrhosis of the liver, spleen and pancreas, accompanied by clinical evidence of diabetes in a greater proportion of cases than we are accustomed to find in simple interstitial lesions of the pancreas.

The origin of the pigment has been variously ascribed to: (1) increased iron ingestion; (2) increased iron absorption; (3) decreased iron output (*a*, inability of the intestines and kidneys to put out iron; *b*, inability of the iron containing cells anywhere in the body to part with their iron); (4) fragility of the iron conveyors (erythrocytes), and (5) specific derangement of the organs that have to do with iron metabolism (liver and spleen).

\* From the Pathological Laboratory of the Bellevue Hospital, New York.

1. Abbott: Pig. Cirrhosis in a Case of Hemochromatosis, *P. Path. & Bact.*, 755, 1901.

2. Fuchter: Hemochromatosis with Diabetes, *Am. J. M. Sc.*, 133:78, 1907.

*Nature of the Pigment.*—1. Hemosiderin: This pigment is distinguished by the fact that it contains iron. Its exact chemical formula is as yet undetermined. It is easily demonstrated by Perl's method, appearing in the form of coarse Prussian blue granules. It is the more important pigment in hemochromatosis. The liver in a marked case of hemochromatosis is literally overrun with it, quantitative chemical determinations showing as much as one hundred times the normal amount of iron.

2. Hemofuchsin: This is an iron-free pigment that does not give Perl's reaction. The formula is not known. It occurs as fine light brown granules. It is never present in great amounts, and, indeed, its very existence has been disputed by Abbott, Beattie and others,<sup>3</sup> their contention being that, due to age, the iron is more firmly bound than in ordinary circumstances, and that by the use of hot reagents and a greater amount of time, the so-called hemofuchsin may be shown to contain iron. In carrying out this test, the frequency with which one encounters green and greenish blue reactions is supposed to add weight to this contention, especially in view of the fact that such green reactions can be turned into the typical Prussian blue reactions by using hot hydrochloric acid and giving the reaction sufficient time. We are inclined to believe that when the proper technic is observed, most, if not all, of the pigment can be shown to contain iron.

*Distribution of the Pigment.*—The organs in which pigment containing iron has been found are numerous. They include the liver, pancreas, lymph nodes, spleen, heart, suprarenals, thyroid, hypophysis, prostate and skin. Small amounts of such pigment occur also in the wall of the gastro-intestinal tract, in the testes, kidneys and bone marrow. The central nervous system and the lungs are comparatively free from it. The great mass of the iron pigment is found in the liver, pancreas and abdominal lymph nodes. Where the pigment occurs in such masses it is both extracellular and intracellular. Usually in those organs in which this extracellular pigment (overflow pigment) occurs we find scarring and connective tissue overgrowth. Since the two processes run parri passu, the indication is that they are related. Confirmatory of this is the fact that while great quantities of pigment are sometimes present in the heart, thyroid, suprarenals and hypophysis, it is entirely within the cells and is unaccompanied by fibrous change.

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3. Beattie: Hemochromatosis with Diabetes, *J. Path. & Bact.*, **9**:117, 1903. Hess and Zurhelle: *Clin. u. Path. Anatom. d. Bronz Diabetes*, *Ztschr. f. klin. Med.*, **62**:344, 1905. Heller: Skin Changes in Bronze Diabetes, *Deutsch. med. Wchnschr.*, **30**:1716, 1907. Simmonds: Bronze Diabetes and Pig. Cirrhosis, *Berl. klin. Wchnschr.*, **46**:531, 1909. Berg: Bronze Diabetes, *Med. Rec.*, **56**:117, 1899.

The site of election of this pigment is apparently the actively functioning cells of the parenchymatous organs. It occurs also in the endothelial cells of the blood vessels and ducts, in the heart muscle cells, and in Kupfer's cells in the liver. The connective tissue cells are also rich in hemosiderin in such organs as the liver and pancreas, but, as Sprunt<sup>4</sup> points out, this is probably secondary to the disruption of the overlaid cells of the parenchymatous organs. The presence of hemosiderin in the connective tissue cells is never seen in such organs as the thyroid, suprarenals and hypophysis, though there may be great quantities of pigment, there is, nevertheless, no evidence of extensive cell destruction.

The pigment which, in the hands of certain workers, has failed to stain blue with the potassium-nitroprussid-hydrochloric acid reaction, the so-called hemofuchsin, is never a very prominent feature of the microscopic picture. It is described as fine light brown granules occurring in smooth muscle cells and also in the connective tissue cells.

*Theories Explaining the Presence of Pigment.*—Of purely theoretical interest is the idea which has been advanced that there may be an increase of ingested iron in the diet. Likewise, there is no proof of an increase in the known constant iron absorption which characterizes normal metabolism.

Turning to the question of whether there is a decreased iron output, we have first to consider a block in those excretory organs which are known to excrete iron. MacCallum<sup>5</sup> has suggested that the fault may lie in the intestines, the specific cells of iron excretion having lost that function. The kidney might likewise share in the iron block. Histological evidence is against such a view, because if such a sievelike action was operative, the iron would be expected to accumulate at the point of obstruction. As a matter of fact, the kidney and intestines in hemochromatosis are relatively poor in iron. In a case of bronze diabetes, Garrod was unable to detect any iron in the urine, stools or bile.

Iron is known to be widely present under normal conditions in the tissues. It enters into the chemical equation of all nucleoproteins, which are essential constituents of all cells. All cells of the body normally, therefore, have a part in iron metabolism, though in some organs they participate more actively than in others. This may be spoken of as a part of their chromogenic function. This fact, taken in conjunction with the known pathologic anatomy, i. e., of a widespread distribution of iron pigment in the cells, gives the basis of the theory

4. Sprunt: Hemochromatosis, *Arch. Int. Med.*, 8:75 (July) 1911.

5. MacCallum: A Textbook of Pathology.

advanced by Sprunt,<sup>4</sup> Parker,<sup>6</sup> Beattie,<sup>3</sup> and others, that some unknown agent injures the cell in such a way as to interfere with or destroy its iron metabolizing or chromogenic function. The cells which formerly metabolized their iron in a normal manner now become depots for its deposit, the machinery for moving it having in some way been injured or destroyed. This is somewhat analogous to the familiar observation of fat accumulation in injured cells.

The erythrocytes are known conveyers of iron in their hemoglobin. The great majority of the earlier writers assumed that excessive destruction of red blood corpuscles was the source of the accumulated iron. This idea was advanced by Von Recklinghausen<sup>7</sup> in his original description of the disease, and has since had the support of such authors as Osler, Abbott,<sup>1</sup> Opie,<sup>8</sup> Marie, Anschütz<sup>9</sup> and others.

Doubt of the validity of this argument is aroused by the fact that there is no anemia associated with hemochromatosis; that the red blood corpuscles are normal in appearance, and to fragility tests, and that spectroscopic examination of the blood serum shows normal hemoglobin. At the same time, there is no reactive change on the part of the bone marrow, and there is no stercobilin and urobilin. Moreover, in severe and chronic anemias there is no comparable generalized pigmentation, as one would expect were the theory of Von Recklinghausen correct.

On the other hand, hemorrhage and purpura have been features in a number of cases. Roth contends that there is an active blood destruction, though in his opinion this does not satisfactorily account for the whole picture. He cites cases with the blood picture and clinical findings of pernicious anemia. The fact that the majority of the cases show no blood change he explains on the ground that there is an active compensatory erythrocythemia. Roth claims to have seen in the spleen and lymph glands small, irregular forms of red blood cells as well as young and immature cells. Rössle<sup>10</sup> demonstrated the

6. Parker: Case of Bronze Diabetes, Brit. M. J., **2**:1052, 1903.

7. Von Recklinghausen: Ueber Hemochromatose, Tagebl. d. Versammel. d. Naturf. u. Aertzte, 324, 1889.

8. Opie: Hemochromatosis and Bronze Diabetes, J. Exper. Med., **4**: 279, 1899.

9. Anschütz: Diabetes with Bronze Skin; Hemochromatosis and Atrophic Pancreas, Deutsch. Arch. f. klin. Med., **62**:411, 1899. Blumer: Bronze Diabetes and Hemochromatosis, New York M. J., **94**:922, 1911. Muir: The Iron Content of the Organs in Bronzed Diabetes (Hemochromatosis), J. Path. & Bact., **19**:226, 1915. Ungeheuer: Ein Fall v. Bronzediabetes und besonderer Berücksichtigung des Pigments, Virchow's Arch. f. path. Anat., **216**:86, 1914. Cecil: A Study of the Pathological Anatomy of the Pancreas in Ninety Cases of Diabetes Mellitus, J. Exper. Med., **2**:266, 1909. McClure: Metabolism in a Case of Hemochromatosis, Arch. Int. Med., **22**:610 (Nov.) 1918.

10. Rössle: Phagocytosis in Hemochromatosis, Beitr. z. Path. Anat. u. Allg. Path., **41**:181, 1907.



phagocytosis of the red cells by parenchymatous cells. He explained the disease on the basis of injury to capillary walls with numerous minute scattered hemorrhages.

There is still another possibility, however. It is the consensus of opinion that dead red blood cells are disposed of in a definite way, that is to say, they are destroyed by the spleen and their useful elements, particularly the iron, is stored or resynthetized by the liver. In this connection it is significant that the great mass of the iron accumulation in hemochromatosis occurs in the liver. From this point of view it has been easy for many authors to assign the burden of the responsibility to disturbances of the hepatic function. The presence of pigment elsewhere they assume to be the result of transportation of pigment from the liver, although the method of transportation has not been demonstrated. This does not explain the relatively great quantity of iron in the pancreas and the spleen.

For our own part, we are inclined to agree with Roth, Abbott and others, that there is some toxic agent at work which simultaneously produces injury to the erythrocytes and to the cells of the parenchymatous organs. There is then more circulating iron than in normal conditions, making for its greater accumulation in injured cells.

*The Relation of Cirrhosis.*—The sequence of events in the liver merits careful consideration, since it is the scene of most extraordinary changes, notably in the form of massive and diffuse accumulations of iron pigment and accompanying connective tissue overgrowth. There are three possible explanations of the changes occurring in the liver:

1. That pigment is deposited and that there is a reaction to a foreign body in the form of connective tissue proliferation.

2. That the cirrhosis has so injured the cells that they become a ready depository for excess mobile iron.

3. In common with other cells of the body the liver cells have sustained toxic injury. In reacting to this, connective tissue is laid down precisely in the same manner as we are accustomed to conceive in cirrhosis of the ordinary type. Synchronously with this, is the deposition of iron representing the unperformed work of the injured cells of the liver in the metabolism of iron.

A certain proportion of all uncomplicated cases of cirrhosis of the liver, if examined for iron-containing pigment, give Perl's reaction. We found four cases among the necropsy protocols of the 5,000 Bellevue Hospital records that were marked enough to suggest hemochromatosis, although the remaining organs were not pigmented. Abbott cites Kretz's twenty-six cases of cirrhosis of the liver with iron pigment present in fourteen of them. In our cases we have found fibrous changes associated with massive extracellular collections of pigment.

The relationship of hemochromatosis to diabetes mellitus constitutes a problem of interest and importance, particularly with reference to the changes in the pancreas. Thus, in the great majority of all cases of bronze diabetes which have appeared in the literature of medicine, pigmentary or other alterations in the islands of Langerhans were described as totally lacking. In diabetes mellitus, as ordinarily encountered, lesions in the pancreas occur in about 88 per cent. of cases, and consist of sclerotic or hyalin alterations in the islands of Langerhans, withdrawal of the secretion of these isolated groups of cells so interfering with carbohydrate metabolism as to permit the continuous excretion of glucose in the urine. In occasional cases, however, the only demonstrable change in the pancreas in diabetes mellitus consists of extensive connective tissue replacement, the islands remaining unaffected. In these circumstances the question arises as to whether the pancreas has anything at all to do with the production of the diabetic changes, or whether the diabetes is to be regarded as of extrapancreatic origin, the sclerotic changes in the pancreas constituting merely an incidental anatomic feature. This interpretation is of interest in connection with the experimental work of Scobolew, who demonstrated that ligation of the pancreatic duct was followed by atrophy and connective tissue replacement of the parenchyma, the islands of Langerhans remaining intact. If, however, the fibrous mass with its embedded islands is now removed, the animal promptly develops diabetes.

In hemochromatosis with diabetes, histologic changes in the islands of Langerhans, such as sclerosis or hyalin transformation, are practically unknown, and to implicate the pancreas as the cause of the diabetes necessitates assuming changes in the islands which are not demonstrable by ordinary histologic methods, since it is obvious that the mere presence of pigment in the interstitium, with or without connective tissue overgrowth, is insufficient to account for the metabolic disturbances in question. That insular changes of the sort indicated do exist has been shown by Symmers,<sup>11</sup> who, in the islands of Langerhans of alcoholic subjects, demonstrated the presence of extensive fatty changes, using, however, special stains to bring them out, such as sudan III. In ordinary hematoxylin and eosin preparations the islands appear to be normal. Symmers, correlating these histologic changes in the islands of Langerhans in alcoholic subjects with the known fact that alcohol habitués are intolerant of sugar and excrete it in the urine when fed it in slightly excessive quantities, accounts for the intolerance on the basis of definite anatomic changes in the islands of Langerhans.

11. Symmers: The Occurrence of Fat in the Islands of Langerhans, *Arch. Int. Med.*, **3**:270 (Feb.) 1909.

All things being considered, however, we believe it highly probable that the diabetic changes which are associated with hemochromatosis are dependent on changes outside the pancreas.

*Summary of Cases Reported in the Literature.*—At the time of this writing, eighty-one cases of hemochromatosis have been reported. Of these the records of seventy-five were available for study.

**Liver:** Information regarding this organ was found in fifty-three cases. The liver was generally enlarged. Clinically, it was described as slightly enlarged in 60 per cent., moderately in 10 per cent., and markedly in 4 per cent. No enlargement was made out in 20 per cent. of the cases examined. At necropsy, however, 95 per cent. were recorded as enlarged. Twenty-six cases with exact weights showed an average of 2,400 gm. Cirrhosis occurred in 96 per cent. and iron pigment in all cases. The color of the liver varied from brownish red to chocolate. Ascites occurred in eighteen cases. In the majority of cases the mass of iron pigment was found extracellular in the connective tissue. This was usually an amorphous collection. It also occurred in great quantities in the liver cells, which then tended to show signs of degeneration in their poor staining qualities and rather irregular and pyknotic nuclei. Intracellular pigment was always present in fine brown granules. This pigment could often be demonstrated beautifully in Kupfer cells, endothelial cells of capillaries, bile duct cells, and connective tissue cells. Occasionally a finer and lighter brown pigment which failed to respond to Perl's test could be demonstrated in the vessel walls and the capsule. This corresponds to the so-called hemofuchsin.

**Pancreas:** Data concerning the pancreas were obtainable in sixty-five cases. Varying from golden brown to bronze in color, iron holding pigment was present in all cases. Of fifty-two cases with a record of the amount of connective tissue, forty-eight showed marked fibrosis. The islands of Langerhans were rarely affected. Eighty-five per cent. of the fifty-eight cases with records showed a moderate glycosuria (average of 5 per cent.).

**Spleen:** Clinical data concerning the size of the spleen were obtainable in forty-eight cases. In fifteen cases the spleen was referred to as slightly, twice as moderately, and twice as considerably, enlarged. In the remaining twenty-nine cases it was not felt.

At the time of the postmortem examination, from fifteen cases with available weights we find an average of 400 gm. Pigment on gross examination was only noted occasionally, but on microscopic study a small amount of pigment was usually to be seen. The spleen was usually firm, a few times it was soft.

**Lymph Nodes:** The most marked changes were seen in the abdominal nodes. The fact that such nodes are in the line of lymph

drainage from the liver and pancreas has been used as an argument in favor of the idea that there is an active transportation of pigment. Thirty-five of forty-four cases describe massive collections of iron pigment; in some cases this was very extensive, replacing the structure of the organ. There was usually marked evidence of fibrosis. Grossly, the glands were enlarged, shading from a brown to a chocolate color, and usually firm. There are instances, however, in which the glands were extremely soft, in some cases actually diffuent.

**Skin:** The microscopic studies of the skin are disappointing because there is a wide disparity between the striking clinical appearance and the postmortem findings. Iron pigment in the skin was usually scant and found only in the sweat glands. It occurred in about one-half of the cases.

**Heart:** In only twenty-two cases among the seventy-five available for study was the heart described. One-half of these showed hemosiderin within the muscle. This was situated intracellularly at the nuclear poles. In one case only did the connective tissue contain iron pigment. Fibrosis of the organ was reported once, and was not of marked degree.

**Kidney:** Of twenty-three cases described in the literature, sixteen showed iron pigment, always in small quantities, within the epithelial cells of the tubules. Only once (Strater's case<sup>12</sup>), was pigment described in the glomerular tuft. Five cases showed another light brown pigment which we believe was iron pigment not properly demonstrated by Perl's stain.

**Gastro-intestinal Tract:** Histologic data were available in nineteen cases. Six cases showed iron pigment in the small intestines situated intracellularly in the depths of the glands. Twelve cases showed an iron free pigment in the muscularis mucosa. The duodenum and the first part of the jejunum seemed to be the most favorable site for pigment deposit. The stomach seemed to be a less favorable site than the intestine.

**Suprarenals:** The condition of the suprarenals was mentioned in thirteen cases. Ten showed the presence of iron pigment consistently found in the cortex.

**Lungs:** The lung seems to be one of the organs which is relatively free of iron deposit. Eleven cases gave histologic data. In only two was iron pigment observed and then in very small amounts.

**Thyroid:** Nine cases of the eleven describing this gland showed the presence of moderate amounts of iron pigment. Here, as is usually

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12. Strater: Beiträge z. Lehre v. der. Hemochromatose und ihren Beziehungen z. allgemeinen Hemosiderose, Virchow's Arch. f. path. Anat., **218**:1, 1914.

the case in organs rich in parenchyma, the deposit was in fine granules, situated intracellularly, within the epithelial cells lining the acini. The connective tissue was always reported free of iron pigment.

**Prostate:** The epithelium of the gland cells contained iron pigment in eight of nine cases reported. The connective tissue contained iron pigment in two cases, while in two others, an iron free pigment was described. Sprunt<sup>4</sup> reports a case in which the seminal vesicles and vas deferens were rich in iron pigments.

**Testes:** In eight cases only the testicles were studied for pigment. In two an iron containing pigment was found in the endothelium lining the small blood vessels and capillaries. In six cases an extracellular iron free pigment was seen in the seminal canals.

**Parathyroids:** In only two cases have we found the parathyroid described. Both of these contained iron pigment, moderately once, in the other case in huge amounts. The pigment was intracellular in both.

**Bone Marrow:** The bone marrow was examined in eight cases. It was usually hyperplastic, and in seven cases iron pigment was present both intracellularly and extracellularly. One case showed no pigment.

**Brain:** Cerebral hemorrhage was present in two of the seventy-five cases reviewed. Histologic examination in these cases revealed no iron pigment.

**Hypophysis:** Two cases have been studied as to the presence of pigment in the hypophysis. In both it was observed in the parenchymatous cells and in one in the connective tissue.

#### REPORT OF CASES

**CASE 1.**—Male, aged 50 years, expressman. In the hospital three days. Duration of the disease twenty-one days.

*Past History.*—Never sick in his life. Denies venereal disease. Drinks from four to five beers a day and whiskey in small quantity.

*Present Illness.*—Three weeks ago injured right side in a fall from a wagon. Was unconscious at the time. From that time on was in the hospital complaining of pain in the right side and shoulder. He passed no blood in the urine or stools. His bowels were regular and his appetite fair.

*Physical Examination.*—His skin was dark brown in color and was thought to have a case of "vagabonds' disease." His heart was negative. There were signs of hypostatic congestion at the pulmonary bases which increased until the time of his death. The abdomen was enlarged with gas. The liver and spleen were not felt. He died after three days in the hospital.

*Urine.*—Sp. gr., 1.020; cloudy; acid; no albumin. Casts, red blood cells, leukocytes and sugar present.

*Chemical Blood Examination.*—Carbon dioxid tension normal. Sugar, 471 mg./100. Temperature: From 100 to 106 F.; pulse from 80 to 40; respiration, from 24 to 52.

*Clinical Diagnosis.*—Diabetes. Hemochromatosis. Perinephritic abscess.

*Necropsy Report.*—The body is that of an emaciated male. The conjunctivae are icteric. Skin of face, neck, forearms and hands bronzed. Fifty c.c.

of pericardial fluid. The right lower lobe is the scene of a bronchopneumonia. There are basal adhesions. The liver weighs 2,715 gm. It is brownish red in color and coarsely nodular. Lobules are indistinct. The pancreas is long and thin and brownish red in color. Spleen weighs 920 gm., is dark red in color and grumous. The suprarenals show an enlarged brownish red medulla. The right kidney is larger than the left. The testes are normal. The intestines are normal, except for the duodenum and jejunum. Here the mucous membrane is colored brown. There is fluid in the abdomen. *Anatomic Diagnosis:* Cirrhosis of liver and diabète bronzé; chronic splenomegaly; hemochromatosis; chronic hyperplastic gastritis; suppurative nephritis and perinephritis (right), and suppurative prostatitis and periprostatitis; moderate pial edema; terminal sepsis.

*Microscopic Examination.*—Liver: There is a moderate degree of cirrhosis. Coarse strands of connective tissue interrupt somewhat the normal architecture of the organ, but there is not the advanced overgrowth noted in some cases. The formed connective tissue is fairly cellular and contains many capillaries and budding and regenerating bile ducts. The liver cells are fairly well preserved. Their nuclei are only slightly smaller than normal and a bit irregular.

Pigment is present in all of the liver cells, but the majority of it is found in massive collections in the connective tissue septums. In the liver cells, the pigment is more or less diffuse, occurring in the form of discrete brown granules, which are not numerous. However, Kupfer cells scattered among them are fairly bursting with quantities of the pigmented granules. Some of the connective tissue pigment can be made out as lying in the cells, some is apparently in the lymph channels; very little, if any, appears in the new formed bile ducts. The greater part of the pigment, as was said, is aggregated together into the extracellular amorphous collections. Practically all of the pigment gives the reaction for iron.

Heart: With Perl's method quantities of greenish blue pigment is brought out in the heart muscle cells. Much of it is an exaggeration of the bipolar arrangement. There is also some amorphous pigment outside of the cells. In the connective tissue and fat there is a small amount of hemofuchsin. The inner coats of the coronaries show the same pigment. There is a slight fibrosis of the myocardium.

Pancreas: There is a fair amount of perilobular fibrosis here. The pigment is chiefly aggregated in this position and is mostly extracellular. There is also pigment in the cells of the acini and in the cells lining the ducts. The islands of Langerhans are very few in number and small. With Perl's test most of the pigment stains dark green. That in the gland cells tends to retain its yellow brown color.

Kidney: Cloudy swelling; multiple small abscesses. In a very few of the cells of the convoluted tubules scattered blue reacting granules can be seen.

Spleen: A small amount of pigment diffusely scattered can be observed. It reacts positively for iron, and lies in the mononuclear cells for the most part. The connective tissue fibers of the capsule are encrusted with iron salts.

Suprarenals: The glomerular zone shows a massive intracellular collection of iron reacting pigment. There is only the slightest amount of pigment in the reticular zone. The pigmentation is entirely confined to the cells.

Skin: There is a small amount of yellow pigment in the cells of the papillary layer and also in the connective tissue of the walls of the veins. No reaction for iron is obtainable.

Intestines: A beautiful contrast is seen in this section between the blue iron containing pigment in the basal cells of the ducts and the fine yellow granules in the muscularis mucosa, which do not give the iron reaction.

Prostate: Normal.

Testes: Show no pigment and are apparently normal.

CASE 2.—Male, aged 49 years, clerk; in the hospital seven days. Duration of the disease six months.

*Past History.*—Diseases of childhood. No illness for ten years. Has dizzy spells. Venereal disease denied. Drinks a little beer but no whiskey.

*Present Illness.*—For six months he has had thirst and polyuria. During this time his private physician has found sugar in his urine. He dieted and lost thirty-five pounds. A roentgen-ray examination of the liver six months ago was said to show carcinoma of that organ. For two months his abdomen has been getting larger.

*Physical Examination.*—The face is a dusky hue. Collateral circulation established over the body. Heart is negative. Lungs show congestion at the bases. The abdomen is large and contains fluid. The liver can be felt 21 cm. below the costal margin. It has a roughened border. There are no enlarged lymph nodes. He grew gradually worse, complaining very little and died seven days later.

Urine: Sp. gr., 1.035; cloudy; acid; no albumin present; no casts. Leukocytes and sugar present.

Wasserman: Negative.

*Chemical Blood Examination.*—Carbon dioxide, 86. Sugar, 300 mg. per 100 c.c.

*Clinical Diagnosis.*—Diabetes; carcinoma of the liver.

Temperature: From 97 to 98 F.; pulse, from 78 to 120; respiration, from 20 to 26. Blood pressure, 130/85.

*Necropsy Report.*—The body is that of an emaciated male adult. The face and neck are bluish. Heart muscle is brownish in color, flabby and the wall is thin. The lungs show small tumor nodules on the pleural surface. The liver is very large, weighing 5,085 gm. It is brownish red in color and finely granular. On section it shows multiple tumor nodules throughout. The bile is tarry green in color. The pancreas is larger than normal and there are tumor nodules throughout it. It is reddish brown in color, and the connective tissue appears to be increased. The spleen is normal in size and brownish in color. The connective tissue is apparently not increased. The follicles cannot be seen. The lymph nodes at the hilum of the liver as well as those lying retroperitoneally present a peculiar appearance. They are reddish brown in color and almost diffuent. The kidneys are normal, except for a slight brownish color. The suprarenals show a dark brown cortex. The esophagus, stomach and large intestine are normal. From the pylorus to the ileocecal valve the mucous membrane of the intestine is greenish black in color. The thymus is small and bluish red in color. The brain is normal.

*Anatomic Diagnosis:* Brown atrophy of heart; multiple pleural metastases in lung; primary carcinoma of the liver; hemochromatosis of spleen, suprarenals, kidney, pancreas, retroperitoneal nodes, duodenum, jejunum, ileum. liver; secondary carcinoma of peritoneum with ascites; few metastases in pancreas; multiple pigmented atrophic tibial scars.

*Microscopic Examination.*—Liver: The liver is the site of a primary carcinoma. There is in addition a marked cirrhosis. Iron staining pigment is seen in considerable amounts in most of the remaining parenchymatous cells, also in many of the cells of the new growth. There is a moderate amount of iron staining pigment in the connective tissue both intracellular and extracellular and a small amount of fine yellow pigment in the connective tissue which does not give the iron reaction. The duct cells and endothelium of the blood vessels and sinuses contain practically no pigment.

Pancreas: There is a considerable increase in the amount of interlobular connective tissue. The islands of Langerhans are normal in number and size but some of the cells contain iron pigment. The blue staining iron pigment is seen chiefly in the cells of the acini and the duct cells in fine granules.

In the connective tissue both intracellularly and extracellularly there are amorphous deposits of various sizes appearing as a green pigment with the hematoxylin and eosin stain, and of a faint yellowish-brown tinge with the iron stain.

**Lymph gland:** Huge masses of green pigment taking the iron stain almost entirely replace the pulp. Few lymphocytes remain. The connective tissue septums show only a slight yellowish shimmer with the hematoxylin and eosin stain. With the iron stain all of the connective tissue septums are colored a beautiful Prussian blue, suggesting a diffuse incrustation of iron. The vessel walls are literally pipes of iron.

**Skin:** The hematoxylin and eosin section demonstrates a moderate amount of fine, light brown granular pigment in the cells of the sweat glands. With the iron stain there are a few fine blue intracellular granules and a moderate connective tissue incrustation. There is no pigment in the epidermis or other structures.

**Testes:** In a few localized areas there is a blue staining iron pigment in fine granules. This is extracellular and is situated chiefly in the tunica vaginalis and the connective tissue between the seminiferous tubules. Between the seminiferous tubules there are many large mononuclear leukocytes which contain a considerable quantity of light yellow pigment, sometimes in granules, sometimes diffusely distributed. This does not take the iron stain. Elsewhere the section is normal.

**Epiglottis:** The section is normal, except for quantities of fine granular pigment lying in the cells. There is also a small amount of granular blue pigment in some of the cartilage cells.

**Large Intestine:** A slight scattering of blue granular pigment on the surface of the glands of the mucous membrane is undoubtedly an artefact. There is a slight yellow pigmentation in a few of the muscle cells. Otherwise the sections are normal.

**Prostate:** The cells of the acini contain a moderate amount of granular iron pigment. In marked contrast to this are yellow granules of pigment seen within the spindle cells of the interstitial tissue which do not stain with Perl's method.

**Thyroid:** The acini contain a small amount of colloid and are about normal in size and number. The epithelial cells are loaded with huge amounts of blue staining pigment. In some places iron pigment is seen extracellularly in the connective tissue. There is no other kind of pigment present.

**Lungs:** The lungs contain many erythrocytes and phagocytizing epithelial cells laden with broken down erythrocytes. However, with the iron stain there is no evidence of the presence of hemosiderin. The disintegrated erythrocytes appear as a granular dark brown amorphous material.

**Choroid Plexus:** Most of the cells contain a large amount of finely granular blue staining iron pigment. This is quite uniform.

**Suprarenals:** The suprarenals contain no iron pigment. The glomerular zone contains a moderate amount of intracellular, coarse brown amorphous pigment which does not take the iron stain.

**Kidney:** The kidney section shows the epithelium of the tubules and the glomeruli very much swollen. There is no pigment present with any of the methods of staining used.

**Optic Nerve and Retina:** There is brown pigment in the basal cells of the retina, probably melanin. With the iron stain there is no blue pigment except for a slight incrustation of the connective tissue.

**CASE 3.**—Male, aged 56 years; in the hospital one month; doesn't know how long he has been ill.

**Past History.**—Venereal disease denied. Drinks only a little beer. Pneumonia three years ago.

**Present Illness.**—Patient is stupid and complains of pain in the knees and difficulty in walking. He sleeps well, has no headache, and his appetite is good.

**Physical Examination.**—His skin is a dusky bronze color. Heart and lungs are negative. The abdomen is normal and neither the liver nor the spleen can be felt. The left knee joint is tender. While in the hospital his nose



bled for twenty-four hours continuously. He reports that six months and one month ago, respectively, the same thing happened. While in the hospital, the pigmentation gradually increased and involved the mucous membrane of the mouth. He became dyspneic and drowsy before death.

Urine: Sp. gr., 1.015; clear; acid; no albumin or casts; sugar negative. Was given 30 gm. of glucose without producing glycosuria.

Blood: Erythrocytes, 3,800,000; Hb., 70 per cent.; leukocytes, 10,200; polymorphonuclears, 68 per cent.; slight anisocytosis and poikilocytosis.

Blood Sugar: From 214 to 421 mg. per 100 c.c.

Temperature: From 97 to 99 F.; pulse, from 60 to 90; respiration, from 18 to 24. Blood Pressure: 165/80.

*Clinical Diagnosis.*—Addison's disease.

*Necropsy Report.*—The body is that of an adult male of large frame. The sclerae are icteric. The gums are bluish in color. The skin is somewhat dark in color and there are a few brown spots on the abdomen. The heart is brownish yellow in color and shows on section a moderate amount of scarring. The pericardium contains a moderate amount of hemorrhagic fluid. The lungs are normal. The liver weighs 2,100 gm. It is brownish red in color. The surface is smooth with slight lobulations. The pancreas is large and brick red in color. The lobulations are normal in configuration. The spleen weighs 255 gm. It is brick red in color and grumous. The bronchial and abdominal lymph nodes are enlarged, brownish in color, and very soft. The kidneys are asymmetrical. They are otherwise normal. The suprarenals are normal. The testes are normal. The glans penis is greenish yellow in color. The esophagus and small intestine are normal. The stomach and colon are dark green on the inner surface. The cartilages of the ribs are green on section. The bone marrow is red and active looking. The synovial membranes of the knee joints are yellowish brown in color.

*Anatomical Diagnosis:* Hemochromatosis; emphysema and acute and chronic bronchitis; acute pulmonary congestion and edema; hemopericardium; slight chronic interstitial myocarditis; slight chronic aortitis; chronic perisplenitis, splenic tumor with pigmentation; small right kidney (arterio sclerotic); large left kidney; moderate acute parenchymatous hepatitis; large pigmented pancreas; pseudomelanosis of large intestine; carious teeth, pyorrhea and gingivitis; pigmented synovial membrane in knee with arthritis.

*Microscopic Examination.*—Liver: Bands of connective tissue interlace to form coarse lobulations. The scarring, however, is not extremely marked. The liver cells, on the other hand, stain poorly. They are small and show somewhat pyknotic nuclei. They uniformly contain quantities of dark brown granules. In this case, as in the previous one, the greatest deposits are in the connective tissue. Here it appears as masses of various size lying outside of the cells. The connective tissue cells contain very little. The duct cells are noticeably free. The distribution of the pigment is such that the greatest quantity lies at the periphery of the lobules. Studied for iron the reaction is a dark bluish green color, which is undoubtedly positive. In the walls of the vessels a few fine yellow granules which do not react for iron can be seen.

Pancreas: There is a moderate interlobular and interacinar fibrosis. The acini as well as the islands of Langerhans appear normal. Almost all of the pigment is interacinar, the connective tissue being relatively free. The pigment everywhere appears as pure blue granules, with the iron stain. The cells of the acini, islands and duct cells, contain the largest amount of pigment.

Lymph Nodes: The lymph nodes are almost entirely replaced by brown pigmented cells. Thick trabeculae of connective tissue can be seen everywhere. The germinal centers in the small nodes contain the pigment, while at the periphery of the lobule, the normal lymphoid arrangement is present. In the nodes with little pigment, the endothelial cells of the sinuses seem to be involved chiefly, but in the large nodes with extensive change, all the cells

become pigmented. The connective tissue stains a pale lavender with the hematoxylin and eosin stain and with the iron stain all the pigment presents a blue color.

Heart: The muscle is markedly thickened.

Spleen: The splenic architecture is maintained with little increase of connective tissue. Arranged fairly regularly about the trabeculae are numerous large mononuclear cells full of brown granular pigment. These large cells are seen also within the pulp, some clumped and some in strands. With the iron stain blue granular pigment is seen in all of the cells of the pulp and in the large mononuclear cells just described. The fibrous elements show a moderate incrustation.

Stomach: The structure is normal, save for a small amount of finely granular blue pigment, situated intracellularly in the epithelium at the base of the glands. It is fairly well distributed in this location throughout the section.

Lungs: The section shows a marked congestion and a slight scarring of the tissue. The interalveolar tissue contains large mononuclear and polymorphonuclear cells which contain anthracotic pigment. There are also numerous large mononuclear cells which contain fine blue granules when stained by Perl's method.

Kidneys: A marked glomerulotubular nephritis is present. No pigment can be seen.

Suprarenals: There is present a fine granular pigment situated intracellularly in the glomerular zone of the cortex. This takes the iron stain. There is no evidence of fibrosis and no pigment is present elsewhere.

Prostate: All the structure of the prostate appears normal. In the blood vessel walls there is a finely granular iron staining pigment situated intracellularly in the connective tissue. No pigment is seen elsewhere.

Bone Marrow: The bone marrow is hyperplastic. Many of the large myelocytes are seen to contain a moderate amount of iron pigment in fine granules. There is none seen elsewhere.

Testes: Structure is normal. No pigment is present.

Aorta: No pigment is present.

CASE 4.—Male, aged 56 years; in the hospital two months. The whole duration of the present illness is eighty days.

*Past History.*—Typhoid fever, fifteen years ago. Neisser infection, several times. Denies syphilis. Drinks seven or eight beers a day and whiskey occasionally.

*Present Illness.*—Has had no appetite for two weeks. Legs have been weak and he has had pain in the back.

*Physical Examination.*—The skin is icteric. There is cyanosis of the face, edema of the conjunctivae, legs and back. The heart shows mitral insufficiency and dilatation. Fluid in both chests. The abdomen is enlarged and contains fluid. The liver and spleen are not felt. The right knee, spine and pelvis are tender, and have been so for two weeks. Both chest and abdomen were tapped successfully.

Urine: Sp. gr., 1.025; clear; acid; albumin, sugar and bile negative. Erythrocytes present.

Blood: Erythrocytes, 3,000,000; Hb., 75 per cent.; leukocytes, 9,000. Spectroscopic examination of the blood normal.

Temperature, from 98 to 101 F.; pulse, 72; blood pressure, 105.

*Clinical Diagnosis.*—None.

*Necropsy Report.*—Emaciated male adult. Skin and conjunctivae icteric. Face and neck brownish. Heart muscle is brown and pale. There is a lobular pneumonia at the right base. There are also basal adhesions. The liver is small. It is greenish brown in color. It is finely and coarsely granular. The pancreas is large and flabby. It is coffee colored. The peripancreatic and

retroperitoneal nodes are anthracotic and cheesy. Kidneys, adrenals, testes normal. Thyroid shows no alteration. Bile stained clear fluid in the abdomen. Elevated yellow foci over the entire peritoneum.

**Anatomic Diagnosis:** Atrophic cirrhosis of the liver; ascites, icterus, chronic granular peritonitis; chronic hyperplastic perisplenitis; brownish pigmentation of pancreas and retroperitoneal lymph nodes; chronic adhesive pleurisy, emphysema and chronic bronchitis; tuberculous lymphadenitis of peripancreatic and retroperitoneal lymph nodes; lobular pneumonia; multiple erosions of gastric mucosa; scoliosis, osteoporosis general and fragilitas ossium; esophageal varices with melena.

**Microscopic Examination.**—Liver: There is a moderate grade of cirrhosis. The capillaries throughout the liver are tremendously dilated. The liver cells are swollen and stain badly and there is a rather widespread round cell infiltration which is particularly marked under the capsule. With hot hydrochloric acid and potassium ferrocyanid most of the pigment gives the iron reaction. This case is remarkable on account of the fact that practically all of the pigment occurs intracellularly. It is found in both liver and connective tissue cells. Striking also is the amount of pigment that is to be found in the endothelial cells of the capillaries and also in the lining cells of the bile ducts. The findings in the liver in this case suggest a rather more acute termination than occurred in the others.

**Thyroid:** The acini are filled with colloid. The gland cells are crowded with iron holding pigment. There is no evidence of injury to the parenchymatous cells. The connective tissue is normal in amount and is the scene of no pigment deposit.

**Lymph Nodes:** The mesenteric nodes show the presence of a chronic tuberculosis. There are quantities of brown pigment, chiefly extracellular. Some pigment, however, is to be seen in the large mononuclear cells. Studied by Perl's method, most of the pigment gives the dark green color, and lies in coarse amorphous clumps. That which is still granular and within the cells stains blue.

**Spleen:** There is a marked thickening of the capsular connective tissue. Most of the pigment is found in this location by preference assuming a position near the side of the gland pulp. It also is to be found in the trabeculae. There is relatively a small quantity in the pulp cells. All of this pigment is hemosiderin.

**Intestines:** Nothing of note is to be observed, except the very small amount of pigment that occurs in the basal cells of the glands and in the muscularis mucosa. None of this reacts positively for iron.

**Testes:** In the connective tissue and in the endothelial cells there is pigment. In the supporting cells between the seminiferous tubules there is a small amount of fine yellow pigment. No iron reaction is obtainable.

**Kidney:** There is a mild chronic nephritis. The cells of the convoluted tubules are the site of an inconspicuous pigment collection. Perl's test fails to show the presence of iron.

# ONE THOUSAND ONE HUNDRED FORTY-SIX GOITERS IN ONE THOUSAND SEVEN HUNDRED EIGHTY-THREE PERSONS

SIMON LEVIN, M.D.

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## INTRODUCTION

Obscurity and darkness in the field of medicine excite the profession to research. This applies directly to the goiter question, where much has yet to be learned in order to unearth a causative factor which may act directly or indirectly, but, where possible, a careful study of a large series of persons will add, at least, a stepping stone to the necessary knowledge. In this country, before the last draft of men for our army, no thorough tabulation of thyroid enlargements in relation to large numbers examined, and to so many sections of the United States, could have been accomplished with any degree of accuracy. Previously, these data were collected from irrelevant groups, except in a few instances (O. P. Kimball and D. Marine<sup>1</sup>), but we must centralize our information about a thorough classification of many individuals in definite districts, and eventually, compare cause or causes from different areas. Bircher<sup>2</sup> and others in central and southern European countries have given us their results from such collections.<sup>3</sup>

Therefore, the opportunity appealed to me in the comparative tabulation in the draft which I reported in March, 1919.<sup>4</sup> Since that time, on account of the great many statements made and which are not based on any records as to the relative proportion of goiters at the various ages, in the sexes, in periods of life, etc., I examined 1,783 unselected persons, in 1918 and 1919 living in our community, which lies distinctly in the Great Lakes goiter belt, in their relations to enlargements of the thyroid.

I have chosen the district in Torch Lake and Schoolcraft Townships of Houghton County, Michigan. Here there happen to be three distinct water supplies; first, spring water from the Gregory Springs;

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1. Kimball, O. P., and Marine, D.: Prevention of Simple Goiter, *Arch. Int. Med.* **22**:41 (July) 1918.

2. Bircher: Etiology of Goiter, *Practical Med. Ser., Surgery* **2**:275, 1918.

3. Goyanes: Endemic Goiter and Cretinism in Spain, *Endocrinology* **4**:491 (July-Sept.) 1920.

4. Levin, Simon: Discussion of Goiter in Five Hundred and Eighty-Three Registrants, *J. Mich. M. S.* **18**:98 (March) 1919.

TABLE 1.—THE RECORD OF EXAMINATION OF 1,783 PERSONS FOR GOITER IN TORCH LAKE AND SCHOOLCRAFT TOWNSHIPS, HOUGHTON COUNTY, MICH., IN 1918-1919

Age	Males	Females	Single	Married	Born Here	Born Elsewhere	Total Goiters
1	19	33	52	..	50	2	8
2	23	22	45	..	41	1	12
3	19	25	44	..	40	4	17
4	16	12	28	..	23	5	13
5	26	16	42	..	36	6	19
6	15	17	32	..	30	2	23
7	14	15	29	..	26	3	18
8	21	38	59	..	52	7	42
9	18	24	42	..	33	9	33
10	20	30	50	..	45	5	44
11	18	18	36	..	29	7	29
12	20	37	57	..	52	5	51
13	15	26	41	..	33	8	37
14	24	27	51	..	46	5	43
15	14	21	35	..	30	5	26
16	14	34	48	..	43	5	41
17	24	22	46	..	41	5	39
18	22	24	42	3	42	4	43
19	11	28	37	2	36	3	37
20	16	19	29	6	29	6	28
21	16	12	24	4	25	3	24
22	6	18	19	5	23	1	19
23	10	25	19	16	28	7	28
24	16	23	23	16	32	7	27
25	13	11	7	17	17	7	15
26	13	17	17	13	25	5	23
27	13	14	8	19	17	10	17
28	11	13	8	16	20	4	17
29	10	9	2	17	15	4	12
30	12	21	6	27	21	12	23
31	10	15	7	18	16	9	18
32	12	11	6	17	14	9	14
33	4	14	3	15	9	9	12
34	11	22	1	32	20	13	22
35	7	12	3	16	15	4	12
36	17	12	3	26	21	8	18
37	5	15	0	20	12	8	16
38	10	15	1	24	14	11	15
39	7	14	1	20	11	10	13
40	13	19	3	29	22	10	17
41	11	6	2	15	9	8	10
42	10	14	2	22	8	16	16
43	10	8	2	16	10	8	13
44	15	13	3	25	18	10	14
45	13	12	3	22	15	10	16
46	4	8	0	12	4	8	11
47	7	8	2	13	4	11	9
48	10	12	1	21	3	19	11
49	12	9	1	20	5	16	9
50	4	8	0	12	2	10	6
51	5	6	0	11	0	11	8
52	3	7	0	10	2	8	5
53	5	6	0	10	4	7	6
54	4	2	2	4	0	6	3
55	2	5	0	7	0	7	3
56	7	6	0	13	1	12	6
57	7	2	1	8	0	9	4
58	5	7	0	12	2	10	2
59	1	1	0	2	2	0	2
60	10	6	1	15	0	14	5
61	44	33	2+	66+	2+	31+	19

second, Lake Superior water, and third, well water, which is spring water. The people are Americans, the larger percentage of French Canadian extraction, above the average in intelligence and in living conditions. The unhygienic conditions usually found in the poorer districts are absent. Each home has plenty of sunlight and ventilation and a lot or two for gardening. I am personally and professionally acquainted with nearly every person examined. Therefore, my knowledge of them would be of greater value than a simple school examination of many strange groups, whether adults or children. I have compiled the results as shown in the charts, making them as complete and self explanatory as possible. The charts demonstrate very clearly the numbers and percentages in the various ages and sexes from new-born to 61 years plus, in their social and residential relationship, and various types of goiter found in these individuals. There were 790 males and 993 females; 242 full family records; 714 married and 1,029 single; 1,243 were born here and 538 were born elsewhere. Three hundred and forty-one of the latter lived here fifteen years or more.

The definitions used in these examinations were those usually in use.

*Group 1.*—Simple goiter is one giving no symptoms, except an homogeneous enlargement of both lobes and isthmus that may be small, moderate or large. Six hundred and eighty-two goiters were found to be in this group.

*Group 2.*—Adenoma, whether fetal or adult, is an enlarged thyroid with a circumscribed mass, or masses, occupying any portion or portions of the gland, being single or multiple. These tumors were classified as small, moderate and large. The cystomas could not always be differentiated macroscopically from adenomas, as our living surgical pathologic specimens demonstrate. Therefore, I classified that group as adenomas and cystomas. Four hundred and twenty goiters belong to this group.

*Group 3.*—Colloid goiter is an enlarged thyroid gland, firm, symptomless, except from pressure, all the gland involved. The gland feels firmer, doughier and of a different consistency than simple, having no circumscribed masses. Forty-four goiters belonged to this group.

Exophthalmic goiter was also noted, but the proportion was comparatively small. It is rather surprising that among so many goiterous individuals we see so few cases of true exophthalmic goiter, whereas, it is very common to see hyperthyroidism, especially during puberty and the menopause. I find that adenomas becoming active make up the larger proportion of the latter class. In my operative work, the partial thyroidectomies for hyperplastic adenoma for hyperthyroidism

also comprised a large proportion, which only signified that the danger from this phase predominates in the goiter situation in our section, pressure and cosmetic phases comprising a lesser proportion.

The record of infection in each individual was not complete, although many observations would justify my saying something further in this regard. Cretins are very rare in our community, and cases of hypothyroidism are not common. The two cretins here are members of goitrous families in which the maternal parent had a goiter. The families with definite morons are not common, but during the draft examination I found a few families with several morons in each family whose maternal parent or both parents had developed enlargements of the thyroid. I must grant that the numbers and percentages of goiters startle one on examination of the charts, but my observations can be verified by any capable observer who attends an evening or afternoon entertainment in summer.

TABLE 2.—TOTAL NUMBER OF PERSONS AND DIFFERENT TYPES OF GOITERS

	Total Persons	Total Goiters	Group 1 Simple Goiters	Group 2 Adenomas and Cystomas	Group 3 Colloid Goiters
Males.....	790	355	230	119	6
Females.....	993	791	452	301	38
Totals.....	1,783	1,146	682	420	44

TABLE 3.—PERCENTAGE OF DIFFERENT TYPES OF GOITERS TO THE TOTAL NUMBER OF PERSONS AND SEXES EXAMINED

	Total Persons	Total Goiters, per Cent.	Group 1, per Cent.	Group 2, per Cent.	Group 3, per Cent.
Males.....	790	44.9	29.1	15.0	0.76
Females.....	993	79.6	45.5	30.3	3.8
Totals.....	1,783	64.2	38.2	23.5	2.5

## INFLUENCE OF WATER SUPPLY

The examination disclosed that the numbers and proportions of different types of goiter at the various ages and sexes did not vary with the different water supplies, in spite of the fact that the water from Lake Superior must be considerably diluted, and, therefore, any chemical or active virus must be in proportionate dilution. The spring water comes from bubbling springs from five to eight miles in a crow's path due east from the shore of Lake Superior. The former flows into a lake tributary (Torch Lake) of the latter twenty miles from the intake of the Lake Superior water supply station. An adequate idea of the location and relative distances can easily be acquired by a reference to a map of the Keweenaw Peninsula of Upper Michigan. Space does not permit me at this time to mention the

results of examinations of the various water supplies, but I may add that the waters about the county, whether spring water or Lake Superior water, from various sources, have a constant factor. The relation of calcium to sodium elements is always more than 1:1, and this relationship occurs but rarely in any other water supplies in the United States. The water supply has been given the credit for carrying the positive factor of goiter but in this incident, it does not assist us any in determining it. At some future date this study will continue and further information will be presented on this phase of the subject.

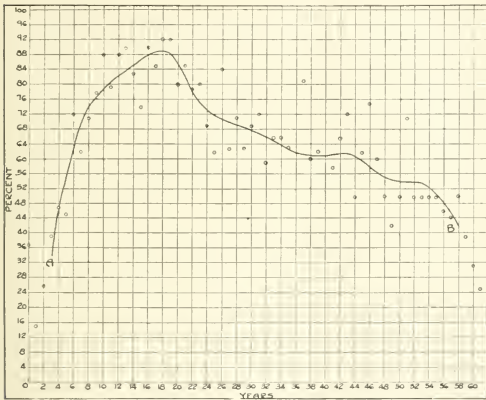


Chart 1.—Outline dots indicate percentage of total goiters to number of persons in each year in the 1,783 examined. AB, mean curve of percentages.

#### INFLUENCE OF AGE AND SEX ON INCIDENCE OF GOITER

The occurrence of goiter in age is so differently influenced by the nature of the sex, that a comparative study of these two factors would be more advantageous. The goiters commence at the first year in about 22 to 26 per cent. of those examined at that age, both sex percentages advancing rapidly towards puberty, much steadier in the female, whose percentage of total goiters in the period from 10 to 15 years being about 94, while that of the male averages about 68.



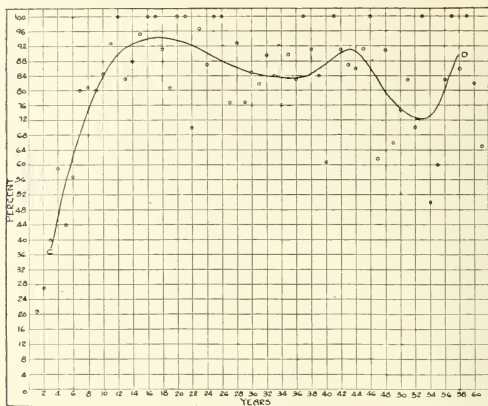


Chart 2.—Outline dots indicate percentage of total goiters to numbers in each year in the 993 females. CD, mean curve of percentages in five year averages.

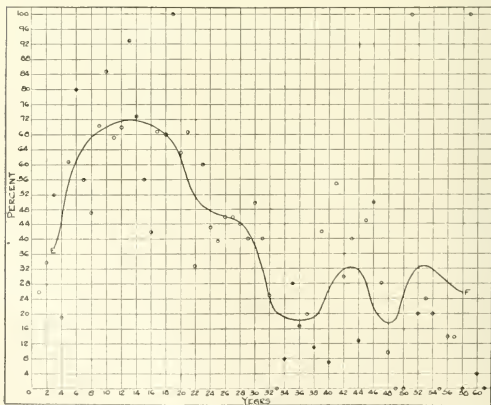


Chart 3.—Outline dots indicate percentage of total goiters to numbers in each year in the 790 males. EF, mean curve of percentages in the five year averages.

The mean curve of the goiter percentages in the female is maintained throughout life above 80 per cent., while that of the male drops very markedly to about 20 per cent. between 35 and 40 years of age, when it gradually rises to the height of 32 per cent. at 42, slipping down later with accidental fluctuations till 20 per cent. is reached near the end of life.

One can readily see that as the functions of the glands of internal secretions are more drawn on by the female at puberty, during child bearing and at the menopause, she has more reason for alteration and growth of this important gland. Therefore, the findings in the percentages demonstrate this fact very clearly. Her incidence of thyroid enlargement is maintained more steadily, not dropping as in the male, after the rise at puberty has been established. In the examination of women at confinement, more than 90 per cent. had their thyroids enlarged from just a palpable mass to a size that interfered with respiration, extending from chin to sternum and latterly bulging the sternomastoid as much as the muscles would permit. Adenomatous masses, simple goiter and normal gland tissue, under ordinary conditions of life, all became hypertrophies during pregnancy. The constant stimulating influence, coupled with the goiter belt irritation, no doubt helps to cause a permanent enlargement of the thyroid gland in these simple and adenomatous goiters.

#### DIFFERENT TYPES OF GOITER

An interesting fact that the tabulation and deduction of percentages of the two important groups of goiters by sex and ages has established, is that in the first half of life in both sexes, till 35 years of age, the maintenance of the large percentages of goiters is due to the simple enlargement of the gland, and that as the age arrives when growths are more prevalent, we see the adenomas and cystadenomas arriving to absolutely maintain the percentage in the female and the male. The curves show that puberty affects the growth to simple goiter earlier than the enlargement of the adenomatous masses. Therefore, the solid line declines at 16 years and the broken line declines at 19 years. Charts 4 and 5 plainly give this wonderful and startlingly clear information. The similarity in time of the appearance of growths corresponds very closely to our idea of growths in other vital parts of the human body, i. e., the cancer period commences at about 35 years of age, and fibromas of the uterus are more marked after from 32 to 35 years of age, etc. No absolute age of commencement of the growths can be established because, no doubt, there were embryonic retention nests potentially amenable to excitation of growth, growing slowly, from the very beginning.

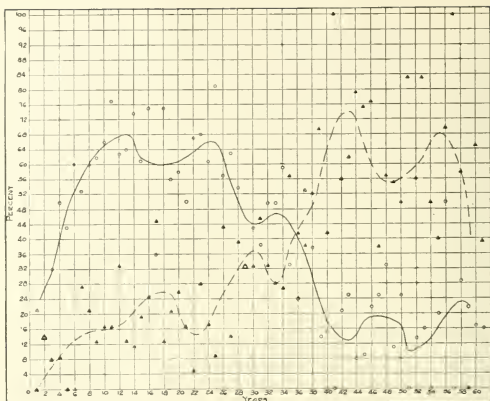


Chart 4.—Different types of goiters in 993 females from 1 to 61 years of age inclusive. Outline dots indicate percentage of simple goiters (Group 1) and solid triangles percentage of adenomata and cystomata (Group 2) to the total females examined for each year. Solid line, mean curve for Group 1; broken line, mean curve for Group 2.

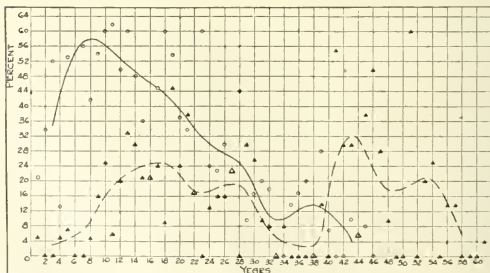


Chart 5.—Different types of goiters in 790 males from 1 to 61 years of age, inclusive. Outline dots indicate percentage of simple goiters (Group 1) and solid triangles percentage of adenomata and cystomata (Group 2) to the total males examined for each year. Solid line, mean curve for Group 1; broken line, mean curve for Group 2.

## PARENTAL RELATIONSHIP OF GOITER

Out of the total numbers examined, mothers alone had goiters in 802 instances, fathers alone in twelve, and both parents 183 times. These figures are only complete as far as they go, because in some families neither the history nor observation could establish data sufficient to note whether the parent or parents had any enlargement of the thyroid.

In the families with four or more children, the family record being complete, it was found that the presence of goiter in both parents resulted in many goiters among the children. Adenomas in both parents, especially the father, meant adenoma in the children. According to Chart 6, which contains records of full families, the influence of the presence of goiter in the mother is four times as great as that in the father. The presence of goiter in both parents leaves the offspring without the smallest possible chance of not developing goiter, if they continue to live in this district.

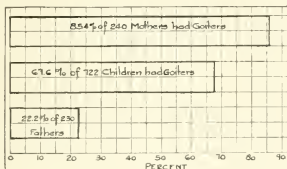


Chart 6.—Percentage of total goiters in 242 complete families with 1,192 persons.

## REPORT OF CASES

1. Family A. P. Father and mother were born in Lower Canada and have adenoma in the right lobes of the thyroid. All the children, four girls and two boys, were born here, living here always. The eldest, a girl, aged 18, has a small simple goiter, but all the other children have adenomas in the right lobes, varying in size from small to large.

2. Family P. M. Father and mother born in Canada and had nine children, eight boys and one girl, all born here, living here always. The father has a small right adenoma, the mother has large multiple adenomas, and the four older children all have from small to moderate sized adenomas, the five smaller ones having small simple goiters.

3. Family L. P. Mother and father born in Canada and had eleven children, six boys and five girls, all born here, living here always. Parents both have adenomas of the thyroid and all the children, except a boy, aged 6, who has an adenoma, have from small to moderate sized goiters.

4. Family E. C. Father and all the children born and always lived here. The mother was born in Arkansas. Mother and father have large and multiple adenomas, respectively, and the children, seven boys and five girls, all except a 2 year old girl, have goiters (three have adenomas, and the others simple goiters).

There is, no doubt, an influence in the mothers with large exuberant thyroids to give birth to infants with enlarged thyroids. Some of the latter are large enough to cause distinct pressure.

In my experience of nearly twenty years in this section, I have never seen a nongoiterous mother bear a goiterous child, but many women with goiters, whose thyroid and goiter enlarged immensely during pregnancy, bore children with distinct enlargements of the thyroid, and, furthermore, nearly all of her children were born with the same enlargement of the thyroid. We can, with reason, draw the conclusions that influences that mean enlarging active thyroids in the mother are carried through the placenta, causing a corresponding enlargement of the fetal thyroid, and also, that no doubt it is of a chemical nature acting positively or negatively. An interesting point is that these large fetal thyroids disappear in from seven to fourteen days after birth, even though the child is nursed by its mother. Therefore, this transmitted influence passes through the placenta and not in the mammary secretion, the child acquiring it later in life. Some of these children at birth have the appearance of cretins with short noses, short stubby hands and the expression of idiots.

#### INFLUENCE AND LIABILITY OF DEVELOPMENT OF GOITER

In reviewing histories of the numbers who suffer from certain types of enlarged thyroids, simple, adenomatous, cystic and colloid goiters, we must conclude that enlargement of the thyroid maintained by living continuously in thyroid belts will be permanent. These glands can only be treated by surgical intervention. This applies more directly to adenomas that have the potentiality of varying in size and becoming plain tumor masses and thyrotoxic.

One thousand two hundred and twenty-three persons were born here and 538 were born elsewhere. Of the latter, 341 lived here fifteen years, 54 lived here from ten to fourteen years, 68 lived here from five to nine years, and 75 from one to four years, inclusive. This makes more than 80 per cent. of the total number subjected to the same local influence by birth or by residence for fifteen years or more. Therefore, if one were born elsewhere in a non-goiterous region and moved to this district, the liability of becoming goiterous would depend on the length of residence and the age of attaining the same. Therefore, we may deduce from these figures and other observations that, being born or acquiring a residence of fifteen years or more here, would entitle one to an enlarged thyroid according to the percentages for that year (Charts 1, 2 and 3). The danger, if the individual continued his residence, increases inversely with the age of attaining the latter.

The liability of goiters developing in persons born here is as follows: Females, aged 13 years and over, 80 per cent.; males, between 13 and 35 years, 66 per cent., and males between 35 and above, 45 per cent. (Charts 2 and 3).

The liability in Group 2 is as follows: Females from 5 to 35 years, 20 per cent.; females, 35 years and above, 62 per cent.; and males from 5 years and above, 20 per cent. (Charts 4 and 5).

#### RELATION OF INFECTION

In analyzing those who have focal infection and develop enlargements of the thyroid, whether becoming toxic or not, I am not free to believe that infection alone, nor the infective agent, causes goiter. The presence of infected teeth, or infected hypertrophied tonsils, or contagious diseases, or other infections will cause in thyroid patients, thyroiditis, enlargements of adenomas, or toxic symptoms, occasionally. The infective agent very rarely does this directly, but the focal toxemia causes a secondary effect on the thyroid. The weight of evidence and observations leads me to conclude that except for a direct thyroiditis, which is not uncommon, thyroid enlargements or thyroid zones are not caused necessarily by direct infective agents. This is said with due respect to the modern writers on the subject who lean toward some infective agent in itself being responsible for thyroid zones. The future will settle the question whether direct infection, or intestinal toxemia, or just the lack of some element in the soil or water, or uncleanness in the handling of vegetables grown here is, or contains, the causative agent.

The large numbers in our section who are practically normal and healthy otherwise, those who lose their enlargements of the thyroid during absence from this section, and the presence of enlargements which become more marked here than elsewhere during the periods of life when the greatest metabolic changes occur—as puberty, menopause, menstruation and pregnancy—are points in circumstantial evidence that offset much in the infective theory.

Sasaki and McCarrison's experiments with the addition of sublimated potassium iodid in a dilution of 1:5,000,000 to rat feces contradict rather than strengthen the infection theory.<sup>5</sup>

The arguments of Kutschera and Taussig can be explained as easily by soil and water supply in susceptible persons.<sup>6</sup> D. Marine and his associates have done work that is most interesting and instruc-

5. Crotti: Thyroid and Thymus, 1918, p. 264.

6. Crotti: Thyroid and Thymus, 1918, p. 265.

tive.<sup>7</sup> They have found that reduction and prevention of thyroid enlargements can be obtained by the use of 2 gm. of sodium iodid taken in 0.2 gm. doses for ten days twice yearly.<sup>6</sup>

In the families who live here constantly, where there is crowding and plainer, simpler methods of living and poorer hygienic conditions, goiters are more prevalent. This observation has been made elsewhere and corroborated many times.

#### CONCLUSIONS AND SUMMARY

1. It must be recognized that in a zone in which thyroid enlargements occur, as here, there is a normal physiologic hypertrophy, and this should not be called goiter. But to appreciate the various lines of demarkation, much study and astuteness in the differential diagnosis of thyroid enlargements is needed. All adenomas, cystomas and distinct colloid goiters can be classed as nonphysiologic. Simple enlargements may be only a physiologic response to internal needs or external influences,—the latter exaggerating the former. The thyroid gland, no doubt, plays an important rôle in the endocrine hormone in maintaining the balance of metabolism in the body and being prominently located, exhibits its response more markedly than do its associates. But it must be remembered that long continued hypertrophy means permanent enlargement, and one must always keep in mind the definite pathologic potentiality of this most active tissue. When hyperplasia occurs in simple goiter, or adenoma, whether fetal or adult, true exophthalmic goiter and hyperthyroidism may follow. I need not mention the vital organ degenerations that mark their paths.

2. One thousand seven hundred and eighty-three persons, ranging in age from new-born to 61 years, were examined for enlarged thyroids. One thousand one hundred and forty-six had enlarged thyroids with 682 simple goiters, 420 adenomas and cystomata and 44 colloid.

3. The incidence curve shows that goiters increase in both sexes during puberty, dropping to a small degree after the growth of the individual is attained. The curve remains in the female for the child bearing period, going down at about 38 or 40 years, when it rises again for the menopause. In the male, the curve gradually drops till 35 or 40 years, when there is a small rise due to the growths in the glands asserting themselves, the male having no special metabolic change to influence the enlargement.

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7. Kimball, Rogoff and Marine: *The Prevention of Simple Goiter in Man*, J. A. M. A. **73**:1873 (Dec. 20) 1919.

4. Charts 1 to 6, inclusive, demonstrate the occurrence by age and sex of the various relationships of simple goiter, adenoma and cystoma, respectively.

5. The simple goiters maintain the high percentage till 35 years is attained and the adenoma and cystoma sustain the height of the incidence curve after that age.

6. The liability table given is approximately accurate.

7. The various water supplies—spring water or Lake Superior water—influence the enlargements of the thyroids the same.

I wish to thank Mr. H. C. Kenny and assistants for their services on the charts.



VARIATIONS OF ACID CONCENTRATION IN DIFFERENT PORTIONS OF THE GASTRIC CHYME,  
AND ITS RELATION TO CLINICAL  
METHODS OF GASTRIC  
ANALYSIS \*

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The quantitative determination of the variation of gastric acidity during different phases of digestion by the so-called "fractional method of gastric analysis" is presumably based on the assumption that the gastric chyme, after a test meal, is a homogeneous mixture, and that a small portion (from 6 to 10 c.c.), aspirated at fifteen minute intervals, represents the acid concentration of the gastric contents as a whole at that period of digestion. If this above hypothesis is correct, and if it is based on a true physiologic principle, then we should expect the acid concentration of different portions of the remaining gastric chyme to be similar at these different intervals after a test meal. It is my purpose to show that this hypothesis is not based on true physiology, and that the acidity of one portion, as obtained by the fractional method, may differ widely from the acidity of different portions of the remaining contents.

METHOD OF PROCEDURE

After the removal of the fasting contents of the stomach by means of a small, soft stomach tube of the Rehfuess type, the patient is given the Dock test meal, consisting of 30 gm. of dry shredded wheat biscuit and 400 c.c. of water. The tube is then reintroduced forty-five minutes after the meal, and the contents aspirated in 10 c.c. portions in rapid succession until the stomach is empty, the last portion being obtained after the inflation of the stomach with air, the patient lying supine. The acidity of these different portions is determined separately by the Toepfer method of analysis, titrating with tenth normal sodium hydroxid, using dimethylamidazobenzol and phenolphthalein as indicators. Tenth normal hydrochloric acid is used for hydrochloric acid deficit. An equal mixture of all samples is used for determining "the average acidity."

This method is practical and is considered sufficiently accurate for our purpose. Considerable care must be taken in preventing the patient from swallowing saliva, and also from extreme retching during the withdrawal of the gastric contents. Samples containing excess of mucus or of bile should not be used for the examination.

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\* From the Department of Internal Medicine, Washington University School of Medicine.

## RESULTS OF EXPERIMENTS

In my experiments the above method of extraction and analysis has been used in sixty-five cases with varied clinical diagnoses. In a few cases successive test meals were given, and the stomach was completely emptied at  $\frac{1}{2}$  hour, 1 hour,  $1\frac{1}{2}$  and 2 hours: in the remaining cases the contents were removed at forty-five minutes after finishing the meal. In 73 per cent. of these patients the acidity of the first sample varied considerably (from 20 to 102) from the acidity of the

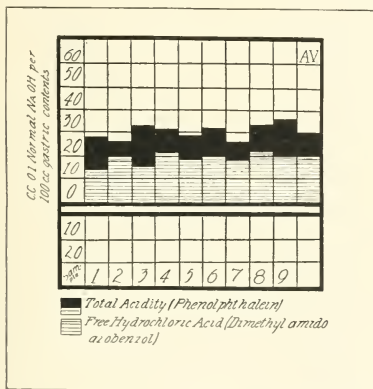


Fig. 1.—Clinical Diagnosis: Constipation. Notice the slight variation of acidity of the different portions of the gastric chyme aspirated in 10 c.c. portions in rapid succession forty-five minutes after a test meal consisting of 30 gm. shredded wheat biscuit and 400 c.c. water.

successive portions. For example, in a patient without clinical evidence of disease (Fig. 1), the acidity of the first sample obtained varied little from the acidity of the successive ones. This, however, is in marked contrast to the results obtained (Fig. 2) in a patient with a perforating duodenal ulcer (twelve hours before operation), where only a trace of free hydrochloric acid was obtained in the first sample at forty-five minutes after a test meal. One of the successive portions (Sample 11) showed a total acidity of 118 and a free hydrochloric acid

of 106. The average of all samples was total acidity, 66; free hydrochloric acid, 55.

It is interesting to note that in a case of supposed achlorhydria (Fig. 3) free hydrochloric acid appeared only in one sample. The other samples, and an equal mixture of all samples, showed a free hydrochloric acid deficit.

In a case of benign pyloric stenosis, successive test meals were given, and the gastric contents were removed in 10 c.c. portions by the above method  $\frac{1}{2}$  hour, 1 hour,  $1\frac{1}{2}$  and 2 hours after the meal. The

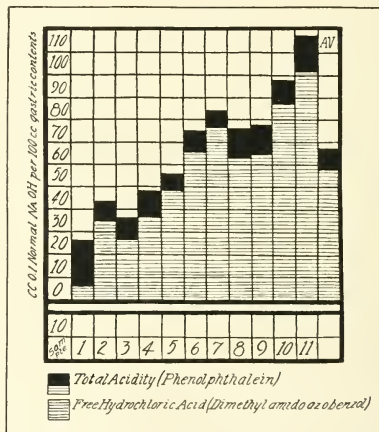


Fig. 2.—Clinical Diagnosis: Perforating duodenal ulcer (confirmed at operation). Stomach emptied by aspirating 10 c.c. portions in rapid succession forty-five minutes after a test meal consisting of 30 gm. shredded wheat biscuit and 400 c.c. water. Notice variations between "sample" (sample 1) usually obtained by the "fractional method," the high point of acid concentration (sample 11) and the average acidity of all samples (last column).

variations of the acidity of different portions of the chyme at these different periods was definite; and if we chart (Fig. 4) the low total acidity at these different periods as one curve, and the high total acidity as another curve, it will be seen how great a variation can be accounted for by the unequal acidity of different portions of the gastric chyme.

## REVIEW OF LITERATURE

Pavlov,<sup>1</sup> in considering the movements of the stomach, was of the opinion that "the contents of the greater stomach remain for hours unmixed, and that the gastric juice digests and dissolves the mass from the exterior inwards."

According to Cannon,<sup>2</sup> a stratification is produced which remains throughout the greater part of digestion, the mass being acted on by the gastric juice from the periphery inward. In consequence, the interior remains long unacidified and here salivary digestion may continue for hours.

Grutzner<sup>3</sup> fed various animals with food, the successive portions of which were of different colors. At varying intervals the stomachs were tied off, removed and plunged into a salt and ice mixture; the mushy contents were frozen solid and cut into sections, always showing a definite stratification.

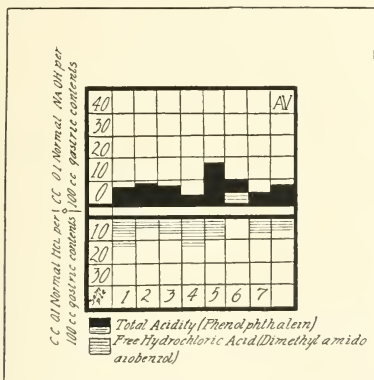


Fig. 3.—Clinical Diagnosis: Chronic Gastritis. Stomach completely emptied by aspirating 10 c.c. portions in rapid succession forty-five minutes after a test meal consisting of 30 gm. shredded wheat biscuit and 400 c.c. water—all samples except one (sample 6) and a mixture of all portions show a free hydrochloric acid deficit (last column).

Prym<sup>4</sup> investigated the behavior of a liquid meal, using Sahli's flour and butter soup. Dogs were given the soup to which blue litmus had been added, and at varying intervals the stomachs were tied off, frozen solid and cut into sections. The central portion and that near the cardia were usually found blue

1. Pavlov: The Work of the Digestive Glands, Ed. 2, London, 1910, Charles Griffin & Co., p. 182.

2. Cannon: The Mechanical Factors of Digestion, London, 1911, Edward Arnold; New York, Longmans, Green & Co.

3. Grutzner: Arch. f. d. ges. Physiol. **106**:463-522, 1905.

4. Prym: Deutsch. Arch. f. klin. Med. **90**:310 (June) 1907.

in color, the rest having been turned red by the hydrochloric acid. Different portions of these contents were cut out and the acidity was determined. It appeared that the degree of acidity was greater at the periphery of the mass than at the center. Prym also administered the liquid meal to a number of patients, and expressed the stomach contents through a double tube with one opening at the tip and the other 10 cm. higher up. In this way he was able to obtain gastric contents simultaneously from different parts of the stomach and found that the two portions varied widely in acidity.

Sick,<sup>5</sup> by a similar method, found that in man, after a liquid test meal (Sahli), the acidity of the pyloric gastric contents varied much from that of the fundal portion: and that, therefore, even after a liquid meal, the stomach contents are far from homogeneous.

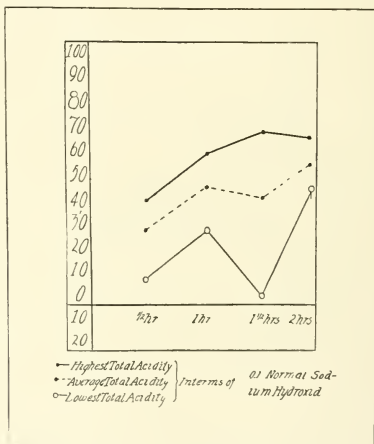


Fig. 4. — Clinical Diagnosis: Pyloric stenosis, benign. The upper curve shows the high total acidity; the lower curve shows the low total acidity, and the broken line the average total acidity of the gastric chyme aspirated in 10 c.c. portions in rapid succession at  $\frac{1}{2}$ , 1,  $1\frac{1}{2}$  and 2 hours after successive test meals consisting of 30 gm. shredded wheat biscuit and 400 c.c. water.

Taussig<sup>6</sup> gave a number of patients test meals and at one hour obtained all the contents possible in the erect posture, and then expressed a portion of the remainder after inflating the stomach with air, the patient lying "prone" or nearly so. The acidity of these two portions was then determined and com-

5. Sick: *Ibid.* **88**:169 (Oct.) 1906.

6. Taussig and Rush: *Boston M. & S. J.* **158**:79 (Jan. 16) 1908.

pared. He found that in a majority of instances these two portions varied in the degree of acidity. In some of the cases the difference was excessive; for instance, in a case of suspected gastric ulcer the first portion of 65 c.c. had a total acidity of 103 with free hydrochloric acid 76, while the second portion of 50 c.c. had a total acidity of 52 and free hydrochloric acid 26.

#### DISCUSSION

It has been shown by the result of experiments, and the work of others, that different portions of the gastric chyme may vary widely in acid concentration: and, therefore, a small sample as obtained in the "fractional method of gastric analysis," or in other methods, where only a small portion of the contents is obtained for analysis, is not, in the majority of instances, representative of the gastric chyme as a whole because the acid concentration of this portion may vary considerably from the highest or lowest acidity of some remaining portion, or the average acidity of the entire gastric contents at that period. The "sample" obtained by the "fractional method" only represents the acidity of the gastric chyme at that moment, in the part of the stomach from where it is obtained; or, in other words, it is dependent entirely on the position of the tip of the tube in the stomach. This position is necessarily a constantly changing one, due, first, to the change of size and position of the stomach while emptying itself through the pylorus and by aspiration; second, the shortening and lengthening of the stomach from gastric contraction; third, the peristaltic waves that tend to carry the tube toward the pylorus.

This explains, in part, the great variety of acidity curves obtained by the "fractional method" in the normal and similar pathologic conditions that in the past have been attributed to secretory variations. What has been said concerning the "fractional method" also applies to all other methods of gastric analyses where only a sample is obtained after a test meal. Therefore, in order to speak of quantitative gastric analysis, the stomach must be emptied completely at a definite time after a standard test meal. The true fractional analysis necessitates the giving of successive test meals and extracting them at different periods: and this, in the majority of instances, is impractical in clinical work.

#### CONCLUSIONS

1. A method of gastric analysis is introduced for determining the variations of acid concentration in different portions of the gastric chyme after a test meal.

2. Experimental evidence is given to show that the gastric chyme is not, in the majority of instances, a homogeneous mixture after a test meal, and that the acidity of different portions may vary widely.

3. In the so-called "fractional" or other methods of gastric analyses where only a small sample is withdrawn, the small portion removed may or may not be representative of the gastric contents remaining in the stomach.

4. Attention is called to a physiologic principle that explains in part the great variety of curves obtained by the "fractional method" in the same individual and in similar pathologic conditions which in the past have been attributed to secretory variations.

I desire to express obligation for the technical assistance of Miss Bertha Isaacs.

# THE NATURE OF SPECIFIC HEMOLYSINS AND A STANDARD METHOD OF PREPARING ANTISHEEP HEMOLYSIN \*

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From the time of the discovery of specific antibodies and their subsequent application to the so-called complement fixation tests, the study of specific hemolysins has especially attracted the attention of numerous investigators.

As early as 1875, Landois,<sup>1</sup> in the course of transfusion experiments, noticed the toxic (hemolytic) effect of alien serums on the erythrocytes of the recipients. But our knowledge of specific hemolysins dates back to 1898, when Belfanti and Carbone,<sup>2</sup> and almost simultaneously Bordet,<sup>3</sup> published their observations on the gradually acquired hemolytic properties of serums of animals injected with erythrocytes of other species.

Following the above observations, more important facts about the multiplicity of such lytic antibodies were disclosed, and so, the general interest was more concentrated on bacteriolysins and other kinds of cytolsins that have to do more directly with the all important question of immunity and anaphylaxis. This resulted in a partial neglect of the equally important question of the nature and mode of production of specific hemolysins.

Hemolysis, in general, is the term applied to the solution or lysis of red blood corpuscles. The term should be applied to some sort of alteration of the red cell stroma permitting the hemoglobin to escape into the surrounding fluids. The stroma may or may not be disintegrated. As this article deals only with specific hemolysins, the question of nonspecific hemolysis brought about by any one of the physical or chemical agencies, such as heating, freezing or thawing, effect of hypertonic or hypotonic solutions, toxins, either bacterial or vegetable, etc., lies outside its scope. Therefore, we shall confine ourselves to specific hemolysins produced under biologic methods by parenteral introduction of alien erythrocytes.

The various methods employed in the production of specific hemolysins are, either in part or as a whole, a repetition of the original method of Bordet, with only a few variations of the dose, of the interval between injections, and of the choice of the site for parenteral introduction of alien erythrocytes. These variations were necessitated by

\* From the Department of Laboratories, Beth Israel Hospital.

1. Landois: *Die Transfusion des Blutes*, Leipzig, 1875.

2. Belfanti and Carbone: *Giorn. della Acad. di Torino*, July, 1898.

3. Bordet, J.: *Sur l'agglutination et la dissolution des globules rouges par le sérum d'animaux injectés de sang défibriné*, *Ann. Inst. Pasteur* **12**:688, 1898.



the difficulty of producing certain hemolysins, such as antihuman hemolysins. A real step toward the understanding of the nature of such hemolysins was taken when washed red cells, instead of whole blood, were injected. This was a logical sequence to our knowledge, that the whole blood was not a simple antigen. Whole blood, besides the various formed elements in it (which by themselves are compound proteins) contains serum, serumalbumin and serumglobulin.

The most generally adopted method of producing hemolysins (antisheep, for complement fixations reactions) is by intravenous injection of sheep cells into rabbits, the amounts varying from 1 to 2 c.c. of a 50 per cent. suspension until four or five such injections are successfully administered, and about a week after the last injection, testing the rabbit serum for hemolysins. The interval between injections varies from three to four days. This method has found general acceptance in the majority of our biological laboratories.

By injecting washed erythrocytes, the possibility of production of undesirable serum antibodies of the nature of serum precipitins has been greatly reduced; but erythrocytes are not a simple antigen, as they are commonly thought to be. Histologically, erythrocytes are composed of a colorless envelope enclosing a solution of hemoglobin. The envelope represents the cell protoplasm and its chemical nature is mainly lipoidal. It is soluble in ether, chloroform and other similar fat solvents. The hemoglobin is a conjugate protein composed of globin, a protein of the group of histons, and hematin, the iron containing pigment. Although the mammalian erythrocyte is devoid of a nucleus, still it contains small traces of nucleoprotein in addition to the above mentioned ingredients.

The relative proportion of the different ingredients is shown in Table 1 taken from Abderhalden (cited after Hammarsten).

TABLE 1.—VARIOUS INGREDIENTS OF ERYTHROCYTES

1,000 Parts Contain		
Water .....		688.00
Organic solids.....		303.88
Inorganic solids.....		8.12
100 Parts of the Dry Organic Matter Contain		
Protein .....	5 to 12	parts
Hemoglobin .....	86 to 94	parts
Lecithin .....		1.8 parts
Cholesterin .....		0.1 part

With such a complex antigen as the erythrocyte, the question naturally arises as to what ingredient is mainly or solely responsible for the production of hemolysin. Ehrlich and Morgenroth<sup>4</sup> produced

4. Ehrlich and Morgenroth: Ueber Haemolysine, Berl. klin. Wchnschr. **21**: 453, 1900.

hemolysins by injecting laked sheep blood to goats. Bordet and Von Dungern maintain that the stroma is the exciting agent. Bang and Forssman<sup>5</sup> were able to produce hemolysins by injecting animals with ether extracts of red blood cells. Nolf attributes mainly to hemoglobin the production of hemolysin, while the stroma, according to him, give rise to hemagglutinins. In a recent study, Kolmer and A. Rule,<sup>6</sup> in corroboration with Vedder<sup>17</sup> were able to produce antihuman hemolysins by injecting washed human cell stroma into rabbits.

#### EXPERIMENTAL WORK

We separated the complex antigenic value of the erythrocyte into its component parts and then investigated each part individually. As it is possible to separate the stroma from hemoglobin—the major antigenic fraction represented in an erythrocyte—the following, rather simple technic, was developed.<sup>8</sup>

After washing sheep cells absolutely free of serum (this takes at least five or six washings in physiologic sodium chlorid solution), the supernatant saline solution was decanted and replaced gradually with sterile 0.4 or 0.5 per cent. saline solution, shaking constantly, until enough hypotonic saline solution was added to hemolyze almost completely the red cells. A few cells should always remain unhemolyzed in order to protect the further destruction of the already hemolyzed cells. These few undissolved red cells are gotten rid of by a few turns in the centrifuge and the opalescent red fluid is decanted free of undissolved red cells. It contains, in suspension, the cell envelopes or the so-called "shadow forms," with some leukocytes in a menstruum of hemoglobin solution.

To separate the stroma from hemoglobin, the opalescent fluid obtained was further centrifuged at a very high speed for 30 minutes until the supernatant fluid was absolutely transparent. Now, the tube showed at its bottom a small amount of a flesh colored mass; this represented the stroma. The fluid portion was decanted and the sediment shaken repeatedly with physiologic sodium chlorid solution and centrifuged until it was free of all the traces of hemoglobin. Finally, the uniform emulsion was made in saline solution of an equal

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5. Bang and Forssman: Untersuchungen über die hämolysinbildung, Zentralbl. f. Bakteriol. u. Parasitenk. **40**:151.

6. Kolmer and Rule: Studies in the Standardization of the Wassermann Reaction, Am. J. Syphilis **4**:484, 1920.

7. Vedder, E.: The Production of Antihuman Hemolysins, J. Immunol. **4**: 141, 1919.

8. Vedder<sup>7</sup> noticed that by passing ordinary illuminating gas through washed erythrocytes, a larger percentage of cell envelopes, 33 per cent., could thus be obtained. As our work antedates that of Vedder, we will give our technic as adopted three years ago.

volume with that of the original blood used. This was placed in a sterile flask and kept aseptic with the addition of a little phenol, enough to make a 0.5 per cent. solution. This constituted the stock antigen of the lipin fraction of erythrocytes.

The hemoglobin fraction was further diluted with saline solution to five times its original volume and centrifugalized repeatedly for from one half to one hour until it was free of all formed elements, when examined microscopically.<sup>9</sup>

After thus separating the two main antigenic fractions of the erythrocyte, the following three series of experiments were undertaken:

Series A, to show the antigenic value of each fraction by itself.

Series B, to show the anaphylactic or toxic value of either fraction.

Series C, to inquire into the possibility of nonspecific toxicity on the part of either fraction.

#### EXPERIMENT SERIES A

*Lipin Fraction.*—To test the antigenic value of the lipin fraction both rabbits and guinea-pigs were used. These animals were injected at regular intervals of two or three days with amounts of stroma to represent from 5 to 10 c.c. of 50 per cent. erythrocyte suspension until four or five such injections had been administered successfully. A week from the last injection, animals were bled to death, no anesthetic having been used for this purpose. The serum thus collected was tested for the following antibodies:

1 Agglutinins and Precipitins: To test for agglutinins and precipitins, of the various dilutions of immune serum shown in the table below, each tube contained 0.25 c.c. and in addition 0.25 c.c. of 1 per cent. washed sheep cells suspension. The tubes were shaken well and incubated at 37 C. for one hour, then left at room temperature and the readings were taken the following morning.

2. Hemolysins: Here, again, of the various dilutions of immune serum, each tube contained 0.10 c.c. to each 0.10 c.c. of 5 per cent. washed sheep cells and the volume of each tube brought up to 0.50 c.c. by adding saline. The tubes were then incubated in a water bath at 37 C. for thirty minutes. After the cells were thus sufficiently sensitized, 0.25 c.c. of a dilution of guinea-pigs serum representing 2 units of complement was added to each tube. The total volume was brought up to 1.25 c.c. by further addition of 0.50 c.c. of saline. Readings were taken after one hour's incubation in a water bath at

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9. It is difficult to get the hemoglobin fraction free of all stroma, for even after a very prolonged centrifugalization, one still finds a "shadow form" in every two or three microscopic fields with the hanging drop method, under 500 diameters.

37 C. The results are tabulated in Table 2. The controls were negative.

3. Hemoglobin fraction: This experiment was carried out only on guinea-pigs. The technic was similar to that used in the lipin fraction experiments. The results are given in Table 2.

TABLE 2.—RESULTS OF EXAMINATION OF IMMUNE SERUM FOR LIPIN AND HEMOGLOBIN FRACTIONS

Agglutinins—Precipitins			Hemolysins		
Serum Dilution	Lipin Fraction	Hemoglobin Fraction	Serum Dilution	Lipin Fraction	Hemoglobin Fraction
1:2	±	++++	1:10	C	C
1:10	—	++	1:50	C	C
1:25	—	+	1:100	C	ACH
1:50	—	±	1:250	C	—
1:100	—	—	1:500	C	—
1:250	—	—	1:1000	ACH	—
1:500	—	—	1:1500	PH	—
1:1000	—	—	1:2000	LH	—

+ denotes the degree of completeness of reaction.

± denotes doubtful reaction.

— denotes absence of reaction.

C denotes complete hemolysis.

ACH denotes almost complete hemolysis.

PH denotes partial hemolysis.

LH denotes little hemolysis.

The lipin fraction, while almost absolutely lacking in hemagglutinogens and hemoprecipitinogens, is very rich in hemolysinogens. On the other hand, the hemoglobin fraction with a rather marked hemagglutininogen and hemoprecipitinogen shows also a weak hemolysinogen. In our opinion, the presence of such small amounts of hemolysinogens is due not to the hemoglobin antigen but to the unavoidable presence of very small amounts of stroma in suspension in the hemoglobin fraction injected, as already mentioned. If, however, the hemolysins produced by injections of hemoglobin fraction is induced by the specific hemolysin-inciting value of hemoglobin, then its nature should be (although not necessarily) different. This is not, however, the case since the conjoined action of both serums as manifested by hemolysins is represented simply by the sum of their respective hemolytic values as if each acted separately.

#### EXPERIMENT SERIES B.

*Determination of Anaphylactic Value of Each Fraction.*—In the course of experiments (series A), it was noticed that animals injected with regulated doses of the lipin fraction never exhibited any toxic reaction to such injections, intravenous for rabbits, or intraperitoneal for guinea-pigs. On the contrary, starting with the third injection,

animals injected with the hemoglobin fraction manifested mild but definite toxic reactions. There were no fatal results either with rabbits or with guinea-pigs. On the supposition that the doses may have been too small to manifest their toxic effects (if at all toxic), a new series of animals was injected with increasing doses of both antigenic fractions, the last injection well exceeding from four to five times the initial dose. Here, again, animals receiving the lipin fraction did not manifest any toxic symptoms. The hemoglobin fraction, on the other hand, manifested varying grades of toxicity, although it was never fatal.

Finally, the original method of Rosenau and Anderson was adopted for producing anaphylaxis. One sensitizing dose of each antigen was injected, and after the completion of the supposed incubation period of approximately twelve days a very large toxic dose, namely, from 10 to 15 c.c. of 50 per cent. erythrocytes, was administered intraperitoneally. Again, the animals injected with the lipin fraction did not manifest any anaphylaxis. On the other hand, the animals injected with the hemoglobin fraction in some cases showed moderately severe anaphylactic symptoms, and in rare instances death occurred.

About two years ago, the question of the cause of sudden death in rabbits injected with sheep erythrocytes for producing hemolysin, was studied. Excluding all cases of death attributable to serum anaphylaxis (as a result of improper washing of erythrocytes or to agglutinated masses in the cell suspensions), a certain number of the animals died with definite anaphylactic symptoms on the third injection, from four to six days after the first injection. This is well within the incubation period. In these cases specimens were obtained by biopsy, either while yet under the shock of anaphylaxis or immediately before the heart had ceased to beat, and their serums were tested for hemolysin. The findings were rather interesting. Such serums invariably showed a high hemolysin content as compared with animals that survived a shock or did not manifest it at all. After careful study the conclusion was reached that the degree of toxicity of such intravenous injections was in direct proportion to the degree of previous sensitization of the animal and the amount of erythrocytes injected. The conclusions to be drawn were that death was either the result of true anaphylaxis, where the ratio of the toxic to the sensitizing dose was very much above the normal limits, or that death was due to a simple nonspecific toxic reaction very much like any other chemical intoxication. If the latter hypothesis were true, then the matter could be explained only on the basis of a sudden flushing of the tissue cells with the toxic products resulting from an immediate dissolution of the erythrocytes injected. This aspect of the question is dealt with in the following third series of experiments.

## EXPERIMENT SERIES C

*Possibility of Nonspecific Toxicity of the Two Fractions.*—Many investigators had already observed the nonspecific toxic effects of intravenous hemoglobin injections. The third series of experiments, where very large single doses of both lipin and hemoglobin fractions were injected to sensitized rabbits and guinea-pigs (with the sole aim of determining the minimal lethal dose of these fractions), failed to corroborate the conclusions of previous investigators.

Of the hemoglobin fraction, doses representing 5 c.c. of straight packed cells were injected intravenously, with only transient toxic symptoms, never resulting in death. As regards the lipin fraction, single doses representing over 25 c.c. of straight packed cells were administered both to rabbits and to guinea-pigs with not even the slightest toxic manifestations. It is possible, however, that the different results may be due to a difference in the product used, as this hemoglobin was a rather pure product, free of stroma or of their deterioration products. At any rate, one thing at least is certain, namely, that the toxicity of red cell injections does not reside in the cell stroma; nor are we absolutely certain that it resides in the hemoglobin.

Landsteiner<sup>10</sup> suggested the possibility that in the intact cells the lipin of the envelopes enter into a chemical combination with the protein of the cell, the result being a complex lipinprotein molecule. There is no reason why such a molecule, when acted on by specific lysins and complement, should not result in anaphylatoxins.

Assuming the above actually to be the case, we must then necessarily admit that laking would alter the biochemical composition of the stroma; for, by injecting such stroma into an alien circulation we failed to obtain anaphylatoxins. On the other hand, however, the generous production of specific antibodies is strongly in favor of the view advocating their antigenic value.

Bang and Forssman,<sup>5</sup> working with ether extracts of erythrocytes, state that by injecting such ether extracts into animals they could produce hemolysins. Landsteiner and Dautwitz, however, attribute the production of such hemolysins to other antigenic substances in such ether extracts, either in solution or in suspension.

We have injected into guinea-pigs lipins extracted with absolute alcohol from dried heart muscle. After the administration of from four to five such intravenous injections, covering a period of from

10. Landsteiner: Weichardt's Jahresbericht 6: 1910.

11. Dautwitz and Landsteiner: Ueber Beziehungen der Lipoide zur Serum-hämolyse, Beitr. z. chem. Phys. u. Path. 9:431, 1907.

fifteen to twenty days, we failed to get any hemolysins in the serums of the guinea-pigs treated.

In all probability, the antigenic value of stroma does not reside in the lipins as such, but, as Landsteiner suggests, in the lipin-protein combination of stroma which may enter into solution or fine emulsion in the organic solvents.

Another explanation of our failure to get anaphylaxis with the lipin fraction of erythrocytes might possibly be found in the assumption of a too vigorous sensitization of the animals with such lipin fractions; as, according to the views of Bordet,<sup>12</sup> the distribution of serum antibodies upon their respective antigens is always uniform. Consequently, where there is an overdose of antigen, the number of antibodies available for each antigen unit will be insufficient to bring about the protein cleavage necessary for the production of poison, that is, anaphylatoxin.<sup>13</sup>

To sum up, whatever be the nature of the hemolytic bodies produced by the injection of cell stroma, the main points to be noted are:

*First*, that by injecting such products we can produce specific hemolysins similar to those produced by whole washed cells, similar at least as far as their hemolytic value is concerned. In fact, by using such hemolytic sensitizers in thousands of parallel Wassermann tests, uniform results on the whole have been obtained.

*Second*, that the production of hemolysins in this way is more economical in the use of animals.

Considering the way this sensitizer is produced, we would, naturally, expect that it should be specific for stroma. This means that the complexity of the antigenic value of cells has been done away with. We believe that a sensitizer, produced in the manner explained, will not in any way be inferior to that produced by the usual method, and in addition will give more specific reactions. We might here say that a sensitizer produced by the method in general use, will contain at least two antibodies, antilipin and antihemoglobin. When such a sensitizer is used for complement fixation tests, in the course of hemolysis part of the complement in each test will surely be absorbed by the hemoglobin antibody when the latter is united with its antigen, namely, the hemoglobin now in solution.

I wish to thank Dr. Max Kahn, the director of the Department of Laboratories, for his many kind suggestions during the progress of this work.

12. Bordet, J.: Sur le mode d'action des antitoxines sur les toxines, *Ann. de l'Inst. Pasteur* **17**:161, 1903.

13. Rosenau and Anderson: A New Toxic Action of Horse Serum, *J. M. Res.* **15**:179, 1906; also, A Review of Anaphylaxis with Special Reference to Immunity, *J. Infect. Dis.* **5**:85, 1908.

# STUDIES ON THE EFFECTS OF QUININ ON THE LIVER, BLOOD CELLS AND URINE OF RABBITS \*

DAVID M. SIPERSTEIN AND MORRIS LITMAN

MINNEAPOLIS

## I. EFFECT OF QUININ ON THE LIVER

In the course of a series of observations on the excretion of bile pigments in the duodenum following the use of quinin, Prof. J. P. Schneider<sup>1</sup> found that the bile pigments of the duodenal contents were markedly increased and that urobilinogen also appeared. He regarded this as an indication that the drug gave rise to pathologic changes in the liver. In a search of the literature we have been unable to find reference to any studies on the effect of quinin on the structure of the liver. The present investigation was, therefore, undertaken at his suggestion to determine whether pathologic changes in the liver could be induced in rabbits by the administration of doses of quinin comparable to those given in clinical practice or whether the drug gave rise to hemolysis *in vivo*.

## MATERIAL AND METHODS

For the present investigation, fifteen healthy rabbits were used. Two of them died as a result of the injections and were discarded. With two exceptions, a 2 per cent. solution of quinin hydrochlorid in a Ringer-Langendorf mixture was used. All injections were made intravenously to assure a greater degree of accuracy.

The rabbits were killed by a blow on the head with a heavy stick. The abdomen was immediately opened and pieces of liver tissue snipped off and allowed to drop into a beaker containing a 10 per cent dilution of liquor formaldehydi solution or Carnoy's fluid No. 1. Paraffin sections, cut at 10 microns, were stained with hematoxylin and eosin, and studied. All the material was treated exactly alike.

## PROTOCOLS

RABBIT 1 (Fig. 1).—Weight, 1,950 gm.; received no quinin; killed as a control. Normal arrangement of liver cells in cords. Cytoplasm is finely granular, no vacuoles. Pigment granules abundant in liver cells.

RABBIT 2.—Weight, 1,850 gm.; received no quinin; killed as a control. Same as Rabbit 1.

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\* From the Department of Pharmacology, University of Minnesota.

1. Schneider, J. P.: J. A. M. A. **74**:1759 (June 26) 1920.



RABBIT 3 (Fig. 2).—Weight, 1,680 gm.; received 0.13 gm. quinin (0.079 gm. per kilo); killed one-half hour after injection. Cords of liver cells greatly narrowed, due apparently to pressure of dilated sinusoids. Sinusoids dilated and filled with corpuscles. No pigment granules in liver cells.

RABBIT 4 (Fig. 3).—Weight, 1,850 gm.; received 0.06 gm. of quinin (0.037 gm. per kilo); killed twenty-four hours after injection. Normal arrangement of liver cells. Very little pigment in liver cells. Bile capillaries hard to find. Vacuoles present in the cytoplasm of many cells (hydropic degeneration?).

RABBIT 5.—Weight, 2,260 gm.; received 0.18 gm. quinin (0.079 gm. per kilo); killed twenty-four hours after injection. Liver cells show normal arrangement. Cytoplasm densely granular with small vacuoles. No pigment in hepatic cells.

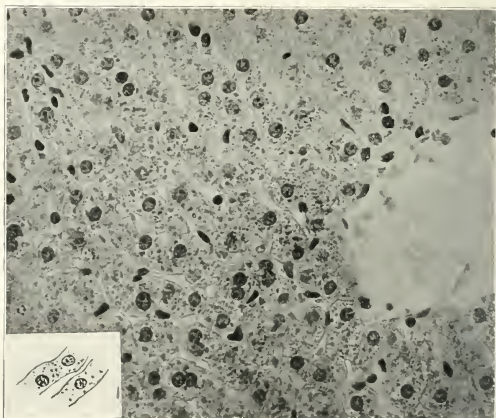


Fig. 1 (Rabbit 1).—Section of normal liver, showing normal structure of cells.

RABBIT 6 (Fig. 4).—Weight, 2,140 gm.; received 0.06 gm. quinin (0.028 gm. per kilo); killed forty-eight hours after injection. Cytoplasm finely granular containing vacuoles of various sizes (fatty vacuoles). Some bile pigment in liver cells.

RABBIT 7 (Fig. 5).—Weight, 1,860 gm.; received 0.07 gm. quinin (0.037 gm. per kilo); killed ninety-six hours after injection. Normal arrangement of cells. Cytoplasm coarsely granular, no vacuoles. Pigment granules abundant in liver cells.

RABBIT 8 (Fig. 6).—Weight, 1,800 gm.; received 0.14 gm. quinin (0.077 gm. per kilo); killed twenty-four hours after injection. Cells have lost their cord-like arrangement. Enlarged liver cells, from three to four times normal in size. Cytoplasm, coarse granules packed at the periphery of cells. Clumps of

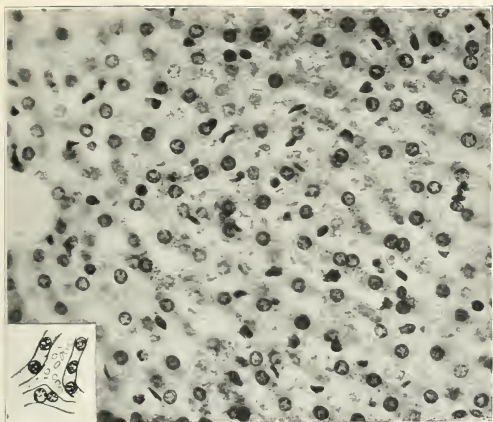


Fig. 2 (Rabbit 3).—Section showing dilated sinusoids and narrowed cords of liver cells.

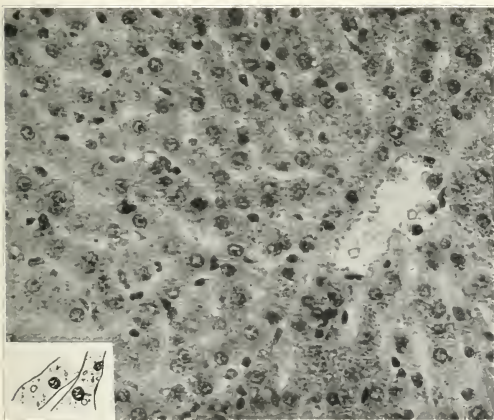


Fig. 3 (Rabbit 4).—Section showing vacuoles in the cytoplasm of many cells (hydropic degeneration?).

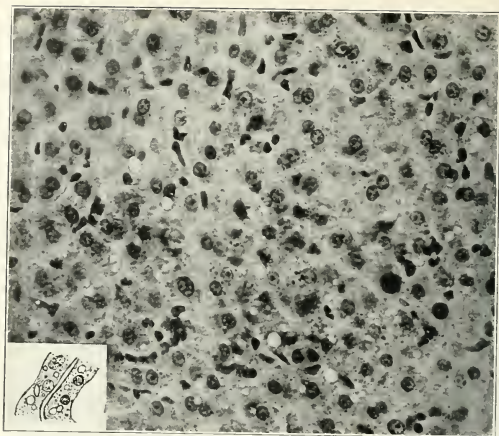


Fig. 4 (Rabbit 6).—Section showing finely granular cytoplasm containing vacuoles of various sizes (fatty vacuoles?).

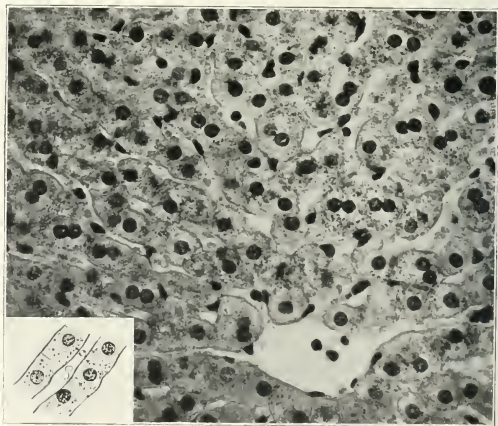


Fig. 5 (Rabbit 7). Section showing liver cells returned to normal.

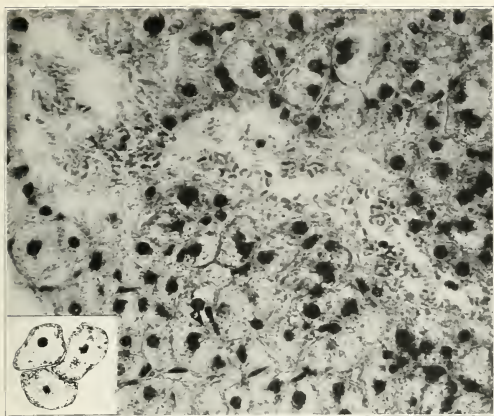


Fig. 6 (Rabbit 8).—Section showing extreme degenerative changes in the cytoplasm of the cells.

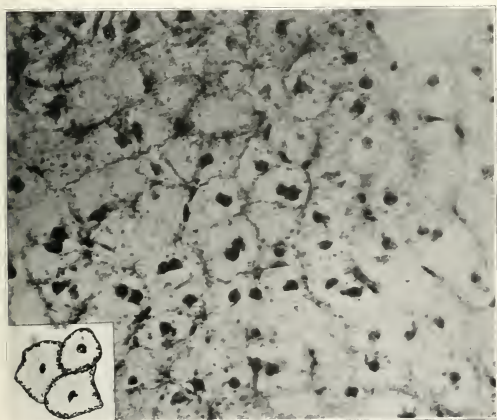


Fig. 7 (Rabbit 11).—Section showing degenerative changes in the cytoplasm of the liver cells.

cytoplasm within the cell. Nuclei, many show pyknotic changes. Sinusoids, difficult to distinguish. The endothelial cells have been pushed together by the enlarged liver cells. Pigment granules not present.

RABBIT 9.—Weight, 2,000 gm.; received 0.12 gm. quinin (0.06 gm. per kilo); killed twenty-four hours after third injection. Same as Rabbit 8.

RABBIT 10.—Weight, 1,380 gm.; received 0.12 gm. quinin (0.087 gm. per kilo); killed twenty-four hours after third injection. Cells retain their cordlike arrangement to some extent. Enlarged liver cells, from three to four times normal in size. Cytoplasm, coarse granules beginning to clump at the periphery of the cell. Nuclei, normal. Sinusoids, variable; normal in some places and difficult to distinguish in others. Pigment granules present. Although treatment was the same as in Cases 8 and 9, this liver was not as markedly affected by the quinin.

RABBIT 11 (Fig. 7).—Weight, 1,450 gm.; received 0.12 gm. quinin (0.082 gm. per kilo); killed 120 hours after last injection. No definite cellular arrangement. Enlarged liver cells (compare with Fig. 6). Cytoplasm, coarse granules packed at the periphery of the cells. Nuclei, show pyknotic changes. Sinusoids, not visible due to the enlarged liver cells. Pigment granules, not present.

RABBIT 12.—Weight, 1,640 gm.; received 0.12 gm. quinin (0.073 gm. per kilo); killed 120 hours after last injection. Same as Rabbit 11.

RABBIT 13.—Weight, 1,720 gm.; received 0.12 gm. quinin (0.064 gm. per kilo); killed 120 hours after last injection. Same as Rabbit 12.

TABLE 1.—SUMMARY OF ALL PROTOCOLS

Animal Number	Weight of Rabbit, Gm.	Injection of Quinin, Gm.			Total Amount Received, Gm.	Intervals at Which Quinin Was Injected, Hrs.	Time of Sacrifice of Animal after Last Injection, Hrs.	Total Amount of Quinin per Kilo Body Weight, Gm.	Corresponding Dosage for Man of 150 Lbs. (67 Kilos) Gm.	Comment
		1st	2d	3d						
1	1,970	....	....	....	....	..	...	...	....	Normal control
2	1,850	....	....	....	....	..	...	....	....	Normal control
3	1,680	0.13	....	....	0.13	..	1½	0.079	5.293	No reaction
4	1,850	0.06	....	....	0.06	..	24	0.037	2.479	Mild reaction; recovery in 5 minutes
5	2,260	0.18	....	..	0.18	..	24	0.079	5.293	Mild reaction; recovery in 7 minutes
6	2,140	0.06	..	..	0.12	..	48	0.028	1.876	Mild reaction; recovery in 5 minutes
7	1,800	0.07	....	....	0.07	..	96	0.037	2.479	No reaction
8	1,800	0.06	0.04	0.04	0.14	24	24	0.077	5.129	No reaction
9	2,000	0.04	0.04	0.04	0.12	24	24	0.06	4.02	No reaction
10	1,380	0.04	0.04	0.04	0.12	24	24	0.087	5.829	No reaction
11	1,470	0.06	0.06	....	0.12	96	120	0.082	5.394	No reaction
12	1,640	0.06	0.06	....	0.12	96	120	0.073	4.891	No reaction
13	1,720	0.06	0.06	....	0.12	96	120	0.064	4.288	No reaction

## DISCUSSION

One intravenous injection of quinin hydrochlorid produced a gradual progressive change in the liver tissue, followed by a slow recovery. At first, there is noted more or less marked active hyperemia. Within twenty-four hours, the liver cells show some mild hydropic changes in the cytoplasm. In forty-eight, this has progressed to a fatty degen-

eration of the cytoplasm. Apparently, this is the end result and repair commences to take place. Ninety-six hours after the injection, the liver is practically normal again, as far as we can determine.

However, when the animal receives more than one injection of quinin hydrochlorid, the effect is much more severe. The liver cell enlarges and become three or four times the size of the normal cell. All definite cellular arrangement is lost. Cytoplasmic changes are very marked, resembling a granular degeneration. Even the nuclei are affected and pyknosis is common. Sinusoids cannot be made out in many of the sections. The poor blood supply which the cells consequently receive may account for some of the degenerative changes. It is to be noticed that injection of quinin at twenty-four and ninety-six hour intervals apparently gives much the same result.

Quinin hydrochlorid administered intravenously in moderate doses to healthy rabbits produces degenerative changes in the cellular elements of the liver.

## II. EFFECT OF QUININ ON THE NUMBER OF BLOOD CORPUSCLES PER CUBIC MILLIMETER

*Material and Method.*—For these experiments rabbits 7, 8, 9 and 10 were used. Amounts of quinin injected are listed in Table 1. Red and white cell counts were made immediately before and 24 hours after injection of quinin, except rabbit 7, on which counts were made five, twenty-four and ninety-six hours after injection. A differential count was made before and after injection, but there were no variations from the normal and details are therefore omitted from this report. (Table 2).

TABLE 2.—EFFECT OF QUININ ON BLOOD CELL COUNT

Rabbit Number	Dose per Kilo, Gm.	Corpuscles	Blood Counts			
			Before Injection	After Injection		
7	0.037	Red	4,088,000	5 hrs. after	24 hrs. after	96 hrs. after
		White	4,775	6,032,000 8,300	6,200,000 5,560	5,456,000 10,158
8	0.077	Red	6,090,000	24 hrs. after 1st injection	24 hrs. after 2d injection	24 hrs. after 3d injection
		White	5,273	8,080,000 7,325	7,970,000 7,000	7,250,000 3,000
9	0.06	Red	5,022,000	6,320,000	6,064,000	
		White	3,276	4,075	4,880	
10	0.087	Red	4,728,000	5,176,000	5,980,000	
		White	5,900	6,625	6,100	

*Summary.*—Within five hours after an injection of quinin we observe an increase in the number of blood cells per cubic millimeter. The increase in leukocytes is nearly proportional to the increase in red



blood cells, as would probably be the case if the polycythemia were due only to a loss of plasma. In spite of the changes observed in the liver, there is no change in the differential count of the leukocytes. This is persistent for the next twenty-four hours, and then declines, so that ninety-six hours after the injection the count approaches the normal. However, after repeated injections the blood count remains high.

### III. EFFECT OF QUININ ON THE URINE OUTPUT OF RABBITS

Rabbits 11, 12 and 13 were used. Details of injection were as shown in Table 1. The animals were fed and watered routinely. They were placed in separate cages especially constructed to facilitate the collection of urine with very little loss or evaporation. The urine of each animal was collected for four successive days before the injection then for four successive days after the first injection and for five successive days after the second injection (Table 3).

TABLE 3.—EFFECT OF QUININ ON URINE OUTPUT

Time	Number of Rabbit	Amount of Urine, C.c.					Total, C.c.	Average, C.c.
		1st Day	2d Day	3d Day	4th Day	5th Day		
Before injection.....	11	235	212	212	260	...	949	237
After 1st injection.....	..	386	355	320	288	...	1,349	339.6
After 2d injection.....	..	376	380	280	270	275	1,581	316
Before injection.....	12	236	190	230	220	...	836	221.5
After 1st injection.....	..	400	355	330	340	...	142	373
After 2d injection.....	..	440	312	218	208	236	1,414	283
Before injection.....	13	160	155	124	206	...	645	161.2
After 1st injection.....	..	180	150	196	276	...	892	297
After 2d injection.....	..	176	140	138	died	...	454	151

Injection of quinin into rabbits produces an immediate and considerable increase in the output of urine. This persists for a day or two and gradually decreases. Repetition of the injection produced a similar effect.

### SUMMARY

Quinin hydrochlorid, administered intravenously, in moderate doses, to healthy rabbits, apparently produces the following results:

1. Progressive degenerative changes in the liver cells which increase with increasing dosage.
2. A moderate transitory polycythemia rendered persistent by repeated dosage.
3. Polyuria.

We wish to express our thanks to Dr. A. D. Hirschfelder, Director of the Department of Pharmacology, for helpful suggestions and criticism during the progress of this work.

## PULMONARY BOTRYOMYCOSIS

### REPORT OF A CASE

F. A. McJUNKIN, M.D.

ST. LOUIS

Botryomycosis is known to veterinarians as a pedunculated fibrous granuloma of horses especially. The growth usually arises in connection with skin surfaces, and often in the cut spermatic cord following castration. However, in the first description of the condition by Bollinger<sup>1</sup> in 1870 an internal organ, the lung of a horse, was the seat of the disease. In 1897, Poncet and Dor<sup>2</sup> identified the infection in a woman in a small growth on the palmar surface of the hand. Although human cases have been reported from France, Italy and Switzerland, it has been observed most commonly in northern Africa and in Morocco where it is said to occur as commonly as actinomycosis.

The gross lesions consist of abundant chronic granulation tissue which is not especially characteristic but which on microscopic examination reveals granules made up of coccus-like organisms embedded in and surrounded by a hyaline matrix. In the chronic inflammatory lesions described as granuloma pyogenicum or pseudobotryomycosis, these characteristic "botryomycotic granules" are not present.

In 1913, Opie<sup>3</sup> studied a case of hepatic botryomycosis in a girl, 11 years of age, which is the first human case with involvement of an internal organ, and appears to be the only instance of the disease in the United States. In this remarkable case a large part of the liver had undergone necrosis with extensive scarring in some portions and with formation of abscesses containing the characteristic "botryomycotic granules" in others. According to Opie, veterinarians in Missouri and nearby states have seen the disease in horses, while reports indicate that it is uncommon on the Atlantic coast.

In 1914, an article on botryomycosis with a review of the literature to that date was published by Margrou,<sup>4</sup> who was able to reproduce in the testicle of guinea-pigs spherical masses of staphylococci analogous to the "botryomycotic granules" by injection of measured quantities of this organism. The conclusion reached by him is that the zooglea-like hyaline matrix in which the organisms are embedded, and the peculiar

1. Bollinger: Virchows Arch. f. path. Anat. **49**:583, 1870.

2. Poncet and Dor: Lyon méd. **43**:213, 1897.

3. Opie: Arch. Int. Med. **11**:425 (March) 1913.

4. Margrou, quoted by Masson.



cellular reaction, do not signify a specific organism but a certain relationship between the resistance of the host and the virulence of the usual staphylococcus.

Masson,<sup>5</sup> in 1918, observed a case of botryomycosis in a gunshot wound with fracture of the femur. The granulation tissue in which the typical granules are present was curetted from the sinus tract six months after the injury. The wound, after being irrigated with surgical solution of chlorinated soda for two weeks, was curetted and healing followed. He concurs in the opinion expressed by Margrou in regard to the staphylococcus nature of the organism, and places emphasis on nonencapsulated masses of the organisms along the Haversian canals of necrotic sequestrums.

Tussan<sup>6</sup> recently observed four cases of botryomycosis of the skin in Morocco; he discusses them only from a clinical standpoint.

The botryomycotic granules made up of mulberry-like masses of gram-positive coccus-like organisms surrounded by hyaline material are fully as characteristic as the "sulphur" granules of ray-fungus infection, and the histologic diagnosis of botryomycosis is certain and easy. Two views are held in regard to the organism, many regarding it as the usual *Staphylococcus pyogenes aureus*, while others express the opinion that it is a specific coccus. Cultures made from the lesions by the different observers on the ordinary media have usually given a growth quite like that yielded by the staphylococcus.

Especial interest attaches to the case here reported because of its occurrence in the same community from which a previous one with localization in an internal organ was reported.

#### REPORT OF CASE<sup>7</sup>

A male infant, four months of age, was admitted to the St. Louis Children's Hospital, Sept. 15, 1920. The father is a painter. The father, mother and other members of the family have been well during the life of the child, and there is nothing in the family history to indicate the source of the infection.

The child was born at home and nursed the mother for three months, during which time it remained well. It has been on various artificial foods since being weaned and has had diarrhea at times.

The baby has always had a hacking cough which has been much worse during the past six weeks. About three weeks ago it had a high fever which continued for one week.

*Clinical Examination.*—The temperature was 99.2 F., respiration 50. The baby seemed quite lively and cried continually in a loud voice. There was a papular eruption over the shoulders which was probably miliariasis.

There was an impaired percussion note over the entire right side and the breath sounds were suppressed and accompanied by fine crackling rales, with

5. Masson: Lyon Chir. **15**:230, 1918.

6. Tussan: Lyon Chir. **15**:241, 1918.

7. The clinical history I have been permitted to use by Dr. Williams McKim Marriott into whose service the case was admitted.

suppressed breathing posteriorly over the left chest. Impression was that of a beginning bronchopneumonia or of an old process clearing up. Examination of heart, abdomen and extremities, negative.

*Clinical Course.*—September 18, the baby had a distressing cough bringing up a seromucous secretion. The temperature remained low. Leukocytes, 20,000 with 62 per cent. neutrophils. September 23, the lungs showed everywhere medium sized crackling râles. The low temperature is certainly peculiar with so much in the lungs.

October 6 it was evident that the patient was steadily growing worse. Glucose and saline solution were given intravenously. The temperature only occasionally reached 101 F. The lung process had been very peculiar all along—many signs with little temperature elevation. It had been considered of probable tuberculous origin by everyone. Von Pirquet test was repeatedly negative.

The child continued to grow worse and died October 8.

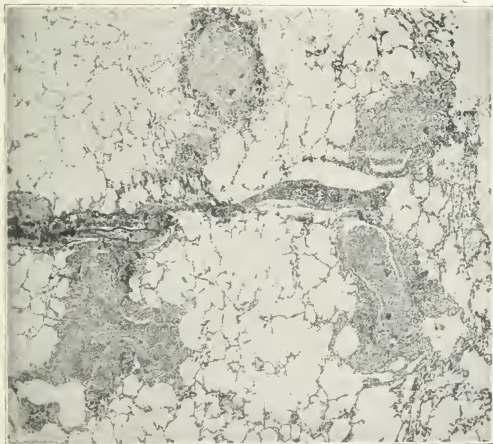


Fig. 1.—A low power photomicrograph to show the areas of bronchopneumonia in which are the dark-staining "botryomycotic granules."

#### REPORT OF NECROPSY

The body is that of a poorly nourished male infant weighing 2,610 gm. There is slight rigor mortis, no lividity and no demonstrable edema; necropsy three hours postmortem.

The peritoneal cavity contains 200 c.c. clear fluid. The stomach and upper portions of the small intestine are greatly distended with gas.

Gross examination of the organs other than the lungs shows nothing definitely abnormal. The myocardium has a slightly yellowish tinge suggesting some deposition of fat. The spleen is firm in consistency and the lymph nodules may be distinguished. The mucosa of the small and large intestines shows nothing unusual. The pancreas, kidneys, adrenals, genito-urinary organs and aorta appear normal.

**Lungs:** Each of the lungs weighs 40 gm. On the pleural surface of both lungs there are centimeter areas of a dark bluish color most of which are somewhat depressed below the surrounding pleural surface. These are present in all lobes but are most conspicuous in the posterior portions of the right lung. On section these irregular areas appear to be airless. The bronchi when cut across exude a mucopurulent material distinctly slimy in character. The peribronchial lymph nodes are not especially enlarged.

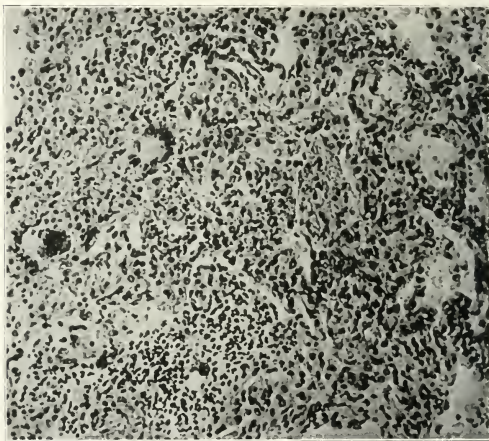


Fig. 2.—A medium power photomicrograph of a pneumonic focus containing two foreign-body giant cells, one incorporating organisms, the other without organisms.

*Histologic Examination.*—The lesions in numerous sections taken from various parts of the lungs are much alike and consist of areas in which the air sacs are collapsed (atelectasis), and of a bronchitis which in many places involves the entire bronchial wall and extends into the surrounding alveolar sacs (Fig. 1). Even with low magnification the latter lesion is quite different from the usual type of bronchopneumonia owing to the presence of giant cells of the type seen in tubercles and of peculiar dark masses which consist of gram-positive coccus-like organisms embedded in a hyaline eosin-staining matrix. In some instances both within the bronchi and outside giant cell forma-

tion (Fig. 2) has taken place about the groups of organisms so as completely to surround them. In Gram-Weigert stains, where the relation of organism and zooglea-like matrix appears to the best advantage, some of the groups are seen to be surrounded by a rather wide zone of hyaline substance the periphery of which is regular or forms small radial projections; others lie free between the cells with little indication of hyaline about them. However, a small amount of pinkish background is seen about some of the groups of a half dozen or more micro-organisms (Figs. 3, 4 and 5).

The exudate in the alveoli and bronchi consists of endothelial leukocytes and neutrophils in about equal numbers. Many of the former have abundant

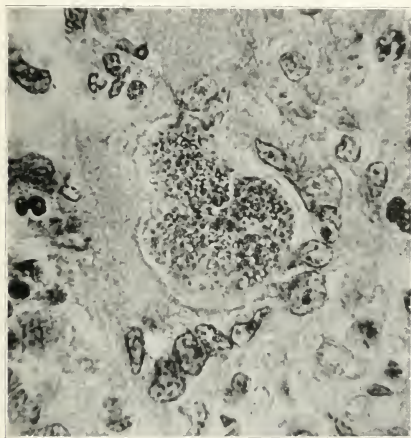


Fig. 3.—Photomicrograph of "botryomycotic granules." Zeiss 3 mm. apochromat. objective and  $8\times$  compensating ocular. Certain ones of the spherical organisms embedded in hyaline are in focus; about the entire mass leukocytes are fusing to form a giant cell.

cytoplasm with fat vacuoles, some have ingested neutrophils, and others have fused to form foreign body giant cells. In the bronchial exudate and in the alveolar sacs there are comparatively few cells of the lymphocytic series but the bronchial walls are the site of an extensive lymphocytic infiltration. In places the epithelium of the bronchi has undergone necrosis and disappeared with extension of the inflammatory exudate into the surrounding air cells. The submucosa of the bronchi is heavily infiltrated with lymphocytes and plasma cells. There are granular foci in the exudate within the bronchi in which most of the leukocytes have undergone necrosis. The alveolar epithelium in the pneumonic areas is intact even in alveoli greatly distended with exudate.

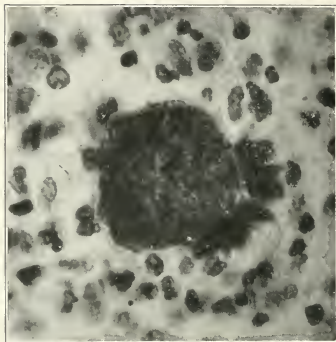


Fig. 4.—The capsule at one side of the mass of organisms stains intensely and presents a radial arrangement.

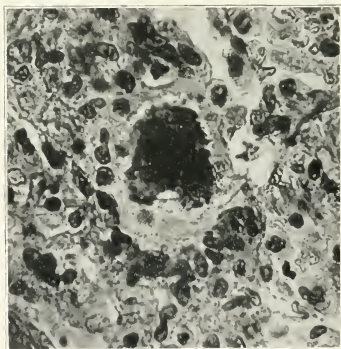


Fig. 5.—Although the homogeneous capsule which lies between the dark mass of organisms and the cells is not stained intensely, it is quite distinct.

The Gram stain of smears of the bronchial exudate made at the time of the necropsy shows further details in regard to the organism. The larger masses of the coccus-like organism are embedded in and frequently encircled by the hyaline matrix, but smaller groups of a half dozen or more often have none of the pink-staining substance about them. There is considerable variation in

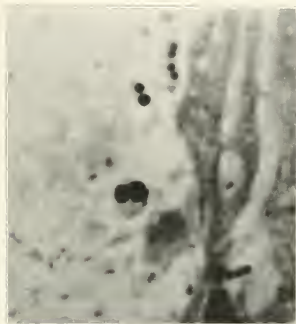


Fig. 6.—Photomicrograph of the organisms in a Gram stain of a smear of bronchial exudate. Zeiss 2 mm. apochromat. objective and 8 $\times$  compensating ocular. Three small groups of the organism in one of which the hyaline has been smeared out on one side and stains positively.



Fig. 7.—A group of the organisms from a part of the smear in which there appears to be a delicate positively staining capsule about each unit of the group. Magnification and staining are the same as in Figure 6.

size and many are less than one-half the diameter of those embedded in the matrix. Groups of two, four, six and eight predominate, and frequently the pairs present a coffee-bean appearance. There are a few chains, the longest consisting of about twenty-four units. In some of the small groups the

hyaline is distinct and about the individual organisms in portions of the smear there are regular pink-staining capsules contrasting with the purplish and more heavily staining organism (Figs. 6 and 7).

Microscopic examination of the other organs reveals no lesions of evident importance. The heart, spleen, stomach and liver are normal. In the mucosa of the intestine there are small collections of plasma cells and an occasional epithelial cell is necrotic and invaded by leukocytes. There is a moderate edema of the kidney with hyaline casts in the tubules. In the intima of the aorta opposite the intercostals the collagen is pushed apart by a small amount of granular material and in this there are a few migrating endothelial leukocytes.

Cultures on blood agar plates made from the bronchial exudate gave a heavy growth of gram-positive cocci which presented the usual appearance of *staphylococcus albus*. Nothing unusual was suspected at the time of necropsy, and unfortunately the cultures taken had been discarded when the lesion was identified from the sections of lung. Smears and sections of the lung stained by the Ziehl-Neelsen method show no acid-fast bacilli.

#### SUMMARY

With the pulmonary symptoms predominant at the beginning of the disease and persisting for several weeks in such a manner as to suggest pulmonary tuberculosis, one is led to think that this case was a primary bronchopneumonia which terminated fatally. It is not perfectly clear, however, that this was the sequence of events.

The histologic lesion is that of a typical granuloma and is one not encountered in infections with pyogenic cocci commonly examined microscopically. The zooglea-like matrix likewise is unique. The appearance of the delicate circle of hyaline material about individual organisms which stains positively and is not a retraction zone suggests a true bacterial capsule and, if confirmed by further observations, especially in connection with animal inoculation, would indicate a distinct species of capsulated coccus.

In conclusion I wish to express my indebtedness to Dr. E. L. Opie who brought to my attention the lesion present in his case and to Dr. H. H. Bell for an examination of the cultures.

## IDIOPATHIC PURPURA WITH UNUSUAL FEATURES

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Many authorities refuse to regard purpura as a disease entity and consider it merely as a manifestation of some other disease. Its extreme rarity is evidenced by the fact that at the Massachusetts General Hospital there were only sixty-four cases in 155,884 medical and surgical admissions; at Johns Hopkins Hospital there were forty-one cases in 18,594 medical cases, and at the Hamburg General Hospital there were seventy-three cases in 100,000 admissions; B. Ramwell<sup>1</sup> saw sixteen cases among 5,256 ward patients. In his table of 258 cases of all kinds of purpura fifty-four were primary and showed arthritis.

In looking over the literature of purpura, it is difficult to find any mention of familial tendencies in this disease. In fact, familial tendencies have been used as a point against purpura in a differential diagnosis from hemophilia, so rarely are they found. There are, however, a few instances reported to which we must add that of the two brothers in this paper. Cousin<sup>2</sup> describes a family in which the disease occurred in three different branches. A case is described by Dohrn in which purpura was transmitted from the mother to her new-born child. Occurrence of the disease in three sisters is reported by Forster. Wagner reported a case of chronic purpura in which paternal uncle of the patient died of acute purpura hemorrhagica. Bauer also describes familial tendencies to a purpuric diathesis occurring in several members at a certain age. The occurrence of these familial cases of purpura rather speaks for the disease as a definite entity. It would seem that there is in certain families an inherent weakness of the germ plasma which manifests itself either in a deficiency of blood platelet formation or in a primary vascular degeneration, or in both these factors (Duke,<sup>3</sup> Wright and Kennicutt,<sup>4</sup> Deny and Ledingham,<sup>5</sup> and Hess.<sup>6</sup>)

1. Branwell: *Clinical Studies* **3**:325, 1905.

2. Cousin: *Ann. de méd. et chir. enf.* **17**: (Oct.) 1913.

3. Duke, W. W.: *Arch. Int. Med.* **10**:445 (Nov.) 1912.

4. Wright, J. H., and Kennicutt, R.: *J. A. M. A.* **58**:145 (May 20) 1911.

5. Ledingham, J. O. G.: *Lancet* **1**:1673, 1914.

6. Hess, A. F.: *Proc. Soc. Exper. Biol. & Med.*, 1917.



## REPORT OF CASES

CASE 1.—Nelson C.; aged 11; schoolboy; born in Canada.

*Family History.*—The family history is entirely negative, there being no history of any similar ailment on either parental side, with the exception of the patient's brother whose case is reported later. The father and mother enjoy excellent health. As far back as they can trace, there has never been a bleeder in the family or anyone with hemorrhagic tendencies.

*Previous History.*—This boy was born normally at full term. He developed normally up to the sixth year after having passed through attacks of measles and whooping cough at the age of 1 year. He had mumps and scarlet fever, complicated by otitis media, at the age of 6. During the whooping cough he would often have epistaxis with paroxysms of coughing but this always stopped promptly and there was never noticed any delay in the clotting of his blood.

The child has been brought up in good surroundings and has had at all times a healthful mixed diet with abundance of fresh vegetables and fruits.

*Present Illness.*—The present illness began about four years ago with a sudden attack of pain in his elbows. They became swollen, stiff and extremely



Fig. 1.—Elbow joint (Case 1) with area of rarefaction in olecranon process; enlargement of epiphyses of humerus and radius, and roughening of medial articular surface.

tender but not reddened. A similar condition later attacked his knees and from then up to the present he has never been entirely free from trouble in some joint, although the knee joints have been the main sufferers. There has been little, if any, fever with the attacks. The swellings appear quite suddenly and appear to distend the tissues about the joints until they are tense and so tender that the merest touch causes excruciating pain. At first they subsided rapidly and seemed to leave the joint no worse for the attack, but of late the knees have become stiffened and somewhat flexed. Simultaneously, the mother noticed that the child "bruised easily" and showed occasional small hemorrhages into the skin. Also on several occasions there would be a sudden swelling, discoloration, hardness and tenderness of the calf muscles. The boy has never had any involvement of the toes, hips, shoulders, sternoclavicular or temporomaxillary joints. There is no history of hemorrhage from the gums, nose, ears, kidneys, bowels or stomach. His blood clots normally after injury

and he seems normal in every other way, except that he has always been pale. With the exception of the pains in the joints he has no complaints whatever.

*Physical Examination.*—This reveals a normal sized boy, pale and with a puffiness of the eyelids. The conjunctiva and mucous membrane of the mouth are free of petechiae. The fundi are both clear. There are shotty posterior cervical and inguinal glands. The lungs are clear. The heart is negative, except for a loud systolic murmur over the pulmonic area. The liver, spleen and kidneys are not palpable. The abdomen is negative. The interest centers in the joint condition, especially that of the knee joints. There is great muscular atrophy of both legs emphasizing the enlargement of the knees. The legs are held flexed. The knee joints are both distended, and there is a thickening of the peri-articular tissues. Riding of the patella is demonstrable. The skin over the knees and on the right side, extending down the back of the leg, is tense and of a bluish-yellow hue due to old blood extravasation. The right knee is extremely tender. There is limitation of motion. No crepitation can be elicited. The right gastrocnemius muscle is tense, tender and hard resembling the so-called scorbutic scleroderma. The skin shows a few small purpuric spots with several larger subcutaneous hemorrhages in the various stages of absorption and discoloration. These are mainly in the forearm, elbow and thigh.

*Laboratory Examination.*—Blood examination shows: hemoglobin, 45 per cent.; red blood cells, 4,000,000; leukocytes, 5,600. Differential count: normal.



Fig. 2. Knee joints in Case 1; anteroposterior and lateral views.

The red blood cells show anisocytosis, poikilocytosis, stippling and polychromatophilia. The blood platelet count is 98,039 per c.mm. The coagulation time is normal. The bleeding time is prolonged to ten minutes instead of being from one to three minutes.

The urine is completely negative. The von Pirquet tuberculin test and the Wassermann test are both negative.

**CASE 2.**—Clarence C., aged 15; schoolboy; born in this country. A brother of the patient reported in Case 1. His complaint was "sore elbows."

*Previous History.*—He was born normally at full term and developed normally. Had attacks of measles, whooping cough, scarlet fever and mumps. Had an attack of jaundice at the age of 5. He had no other acute illness of any kind, and his general health has been good. It was noticed that he "bled easily and freely" on the slightest provocation but no delay in the clotting of his blood was ever present. For instance, on changing altitude, he would suffer with epistaxis, although the changes were not great enough to affect the ordinary person.

*Present Illness.*—His present illness dates from the age of 5 when he had his first attack of joint trouble. This centered in both ankles, which suddenly became swollen and tender. This condition cleared up rapidly only to reappear after a short interval and then the knees were similarly affected. The

patient was unable to walk. He suffered with these attacks up to the present, although lately they have become less frequent and less severe. For the past three years the attacks have been confined to the elbows and he is able to walk without any difficulty whatever. On one occasion, a diagnosis of purulent arthritis was made and a knee joint was aspirated. Bloody serum was obtained. The boy bruised easily and often had large hemorrhages under the skin. He never had an attack of extensive purpura nor was there ever spontaneous oozing from the gums. Six weeks ago he had an attack of severe colicky pain in the right side in the costo-vertebral region radiating downward and forward over the bladder. To use his words, he "felt something pop inside" and



FIG. 3.—Knee joint of Case 1, lateral view, showing definite area of osteoporosis in epiphysis of femur with undue enlargement; thickening of soft structures of the knee joint, commonly seen in repeated blood effusions. Condylar surfaces are rougher than is the case in normal persons.

then he "felt a hot flush through his stomach." Shortly after he noticed that his urine was bloody and stringy. As soon as he began to pass the blood the pains subsided somewhat. This attack lasted for three days. The urine became clear and the pain disappeared. A similar attack appeared four days ago in the left side. The boy's mother noticed no blood in the urine in this attack which was less severe than the previous one. A microscopic examination, how-

ever, showed the presence of red blood cells. In neither attack was there any purpura, nor did the boy show any melena. There was no nausea or vomiting nor was there any exacerbation of his joint symptoms. There have been no other symptoms of any importance.

*Physical Examination.*—On physical examination, we find a bright, normal sized, well-nourished boy. He does not appear to be anemic. The head is entirely negative. The eyes show no petechiae. The fundi are clear of any hemorrhages. Mucous membranes are normal. The gums are healthy and the teeth are excellent. There is slight general glandular enlargement. The tonsils are negative. The heart and lungs are clear. The abdomen shows no abnormality. There is marked left costovertebral tenderness present. The liver, kidneys, gallbladder and spleen are not palpable. The skin shows a few large brown and blue bruises, one over the right eye and one near the left



Fig. 4. Knee joint of Case 1, anteroposterior view, showing small well defined area of rarefaction in epiphysis of tibia. The epiphyseal lines and the shafts of the bones are normal.

elbow. There are a few smaller purpuric spots in the skin of the left forearm. There are no hemorrhages in the muscles.

As in the first case, the interest centers in the joint condition. The left elbow is the seat of an acute process. The joint is very much enlarged and discolored but not especially tender. The bony landmarks are almost obliterated by the effusion into and the distention of the joint capsule. The olecranon process shows as a depression between two large fluctuating bulging sacs. There is limitation of motion in this joint. Both knees are enlarged due to a peri-articular swelling and thickening but they are not tender, there is no limitation of motion nor is there any sign of an effusion at present. There are scars over both knee joints at the site of the previous aspiration. All the other joints are normal.

*Blood Examination.*—Hemoglobin, 85 per cent.; red blood cells, 4,900,000; white blood cells 6,600. Differential count, normal. The red blood cells were normal. The blood platelet count was 204,000 per c.mm. The coagulation time was normal. The bleeding time was ten minutes. The urine showed a faint trace of albumin with many red blood cells, the remains of the last attack of colic.

The roentgenograms of the joint (Figs. 1, 2, 3, 4 and 5) show, in general, an enlargement of the epiphyses of the bones with well defined areas of rare-



Fig. 5.—Elbow joint of Case 2 showing roughening of humero-ulnar articulation.

faction, small roughening of the articular surfaces, as in osteo-arthritis; and in the knee joint, a definite thickening in the soft structures of the joint such as one sees in bloody joint effusions.

*Clinical Course.*—The two patients were seen after an interval of seventeen months' army service. The younger brother had had at least one attack of joint trouble a month during this period. He had also had one severe hematemesis in which he lost almost one quart of blood. This occurred six months

after therapeutic intramuscular injections of whole blood. On my return, I found him with a hemorrhage under the tongue, one under the angle of the left jaw, many purpuric spots over the sternum, shins and ankles, and a fresh hemarthrosis of the wrist. His general physical condition was the same, except that the urine showed albumin, casts and red blood cells.

The older boy seemed much improved. Fourteen months after I saw him he suffered a fracture of the right olecranon. He did not know just how or when it occurred. The bone united readily but two months later he developed a fresh hemorrhage in the same joint. He had also had epistaxis but no bleeding into the skin, bowel, stomach or kidney.

A second feature of these two cases is the occurrence of repeated hemarthrosis in each instance. Some even go so far as to doubt its occurrence in purpura, stating that if the arthritic manifestations are at all marked the case should be classed as a simple purpura with arthritis. According to McCrae<sup>7</sup> no case has been found in recent literature. Wagner<sup>8</sup> searched the literature up to 1886 without finding a single case of purpura in which a large hemorrhage had occurred



Fig. 6.—Elbow joint of Case 2.

into a serous sac. Hoffman found no mention of a single definite instance of hemorrhage into a joint in morbus maculosus. There could be no doubt of their occurrence in the above cases. The sudden painful distention of the joints, the external discoloration and subcutaneous ecchymosis of the surrounding tissues and the result of ill-advised aspiration all go to prove the presence of hemorrhage in the joints. The rapidity of recovery of normal appearance and function were also characteristic in the early years of the disease.

A third rare feature is the association of hemarthrosis with the visceral symptoms described under the name of Henoch's purpura or purpura abdominalis. In typical cases of Henoch's purpura joint pains are associated with cutaneous and intestinal hemorrhages and acute nephritis, often of the hemorrhagic type. The arthritis, however, does not go on to the hemorrhagic stage. Each of these two patients, at

7. McCrae: Osler-McCrae Modern Medicine.

8. Wagner: Deutsch. Arch. f. klin. Med. **39**:431, 1886.

some time in the course of his disease, has shown one or both of these two visceral conditions in addition to joint hemorrhages. Nor is hemorrhage into a joint mentioned as one of the symptoms of peliosis rheumatica by Schönlein in his original description of this condition. This description, although vague, has been taken by most clinicians to include only those cases in which there are fever, malaise, purpura and erythema and joint pains. Barker,<sup>9</sup> however, in his classification of the purpuras, states that often there is hemarthrosis in these cases of Schönlein's disease. The absence of fever, malaise, erythema and pains in



Fig. 7.—Elbow joint of Case 2, posterior view, showing rarefaction in external condyle of humerus.

joints other than those distended by blood, definitely excludes these patients from the peliosis rheumatica group.

Another feature of note is the fracture of the olecranon sustained by the older brother. From the description of the patient this was in all likelihood a spontaneous or pathologic fracture in the neighborhood of a joint that had been the seat of a hemorrhage. If one bears in mind the pathology of this disease, especially with regard to the

9. Barker: *Monographic Medicine* 3: p. 239.

rarefaction it effects in the bone substance, it is quite conceivable how this might happen. It might be well, therefore, to consider purpura as a possible etiology for pathologic fracture.

From a perusal of the literature and a consideration of these two cases it would seem that no strict line can be drawn between the various types of purpura described in our modern classification. Morawitz considers all these diseases of the so-called idiopathic purpura group as being different manifestations of one and the same process. Hoffmann, Litten and other German writers have the same view of the primary purpuras, classing them all as "*morbus maculosus Werlhofii*" of varying degrees of severity. In this group are: (1) *purpura simplex*, with hemorrhages in the skin and subcutaneous tissues; (2) *purpura hemorrhagica*, with hemorrhages of the skin and mucous membranes; (3) *peliosis rheumatica* with cutaneous hemorrhage erythema and joint disease; (4) *purpura abdominalis*, with cutaneous and intestinal hemorrhages and joint pains, and (5) *purpura fulminans*, with cutaneous hemorrhages which run a rapid and fatal course.

The cases here reported partook of features that might allow them to be put in any of the above type, except the last.

The pathology of this condition, when the hemorrhage has been repeated often, is quite interesting. Our knowledge of it has been gained by roentgen-ray study of the living subjects, by operations and by a few necropsies in cases that have succumbed to intercurrent conditions. The hemorrhages occur most often in the knee joint, as trauma is most active here, although other joints may be affected simultaneously.

Following a slight blow or often spontaneously, there develop signs of acute joint affection with joint effusion. The condition may stop here, the effusion be absorbed and the joint heal without change. This, according to the description of König,<sup>10</sup> is the primary stage of the disease. If the effusion persists—secondary stage—it goes on to an inflammation with a fibrinous effusion as in the ordinary tuberculous "white swelling." This condition it simulates almost perfectly, but the roentgen-ray will show that the bone is not involved and that the process is confined to the soft parts of the joint (Love,<sup>11</sup> Carless<sup>12</sup>). In this stage, synovial villae are present as well as defects in the joint cartilages, the changes resembling closely those seen in arthritis deformans or osteo-arthritis. The roentgen ray shows changes in the epiphyseal lines which are zigzag and have a worm-eaten appearance. The condylar outlines are not sharp. The capsule shadow is darkened. There

10. Samml. klin. Vorträge, N. F., Leipzig 36:233-242, 1892.

11. Keen's Surgery 2: p. 362.

12. Practitioner 70:85, 1903.



is bone atrophy with rarefaction of the condyles. Mankiewicz<sup>13</sup> questions whether this is a true osteoporosis or a retrogressive metamorphosis in the architecture of the bony trabeculae. If hemorrhage occurs in a joint often enough, König describes a third stage in which there are contractures, bone and joint changes, thickening of all the periarticular structures and even ankylosis. Ponfick also has described hemorrhages into the bone-marrow. Bowlby<sup>14</sup> thinks these cases resemble osteo-arthritis far more closely than is generally acknowledged. He cannot explain the nodular outgrowths of cartilage, new bone formation, fibrillation of the cartilage matrix and the formation of adhesions all as a result of blood extravasation. The attacks, he states, are different than those exhibited by a healthy patient who is suffering from a traumatic hemarthrosis. He thinks that many bleeders have a special tendency to attacks of acute arthritic inflammation which very closely resemble those of the more severe forms of osteo-arthritis. Barker<sup>15</sup> states that the condition also resembles luetic arthritis.

#### SUMMARY

Two cases of idiopathic purpura are described with the following unusual findings:

1. They showed a familial tendency.
2. Repeated joint hemorrhages occurred in both patients.
3. There was an association of joint hemorrhages with the symptoms of Henoch's purpura.
4. Spontaneous fracture occurred in one case.

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13. Mankiewicz: *Berl. klin. Wchnschr.* **76**:2174, 1913.

14. Bowlby: *St. Bartholomew Hosp. Rep.*, London **26**:77, 82, 1890.

15. Barker: *Monographic Medicine* **4**: p. 95.

# THE PRESENT STATUS OF CARDIODYNAMIC STUDIES ON NORMAL AND PATH- OLOGIC HEARTS \*

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The experimental or clinical investigator who essays to study circulatory problems that directly concern vital phases of medicine is frequently handicapped because certain fundamental data, which are the key to the interpretation of these problems, are not included in our stock of general information. It is desirable, therefore, first to review briefly some recent experiments which, I believe, help to clarify our understanding of the normal contraction processes in the heart. This accomplished, the laws which govern cardiac behavior will be analyzed. Finally, an effort will be made to see how far these laws may be applied in the interpretation of pathologic conditions with which we are confronted in the clinic.

## I. THE FUNDAMENTAL MECHANISMS OF THE HEART RATE

*The Physiology of Auricular Systole.*—The cardiac cycle is generally described as consisting of auricular systole, followed promptly by ventricular systole and diastole. It has long been known that certain quantitative differences exist between the contraction of the auricular and ventricular musculature. Thus, the greater capacity of the ventricles for performing work and their longer contraction period are generally emphasized, even in elementary physiology. Recently, evidence has been adduced which indicates that qualitative differences also exist. The ventricles receive their impulses through the His-Tawara system in such an ordered manner that all parts of the ventricular myocardium are virtually excited at the same time (Garten<sup>1</sup>; Lewis and Rothschild<sup>2</sup>). Consequently, we may assume that the entire bulk of the ventricular musculature begins and ends its contraction at practically the same moment.

It is different in the case of the auricular contraction. A few years ago, Lewis and his associates demonstrated that the impulses developed rhythmically in the sinus node, spread eccentrically over the atrial muscular tissues, exciting in succession each fractionate portion

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\* Lecture delivered before the Harvey Society, New York City, Dec. 11, 1920.

1. Garten: Skand. Arch. Physiol. **29**:114, 1913; Ztschr. f. Biol. **66**:23, 83, 1915.

2. Lewis and Rothschild: Phil. Tr. Roy. Soc. London **206**:181, 1915.

of auricular tissue. In this way, the more distal portions receive their excitation later than those portions more proximal to the cardiac pacemaker.

In 1916, I presented experiments<sup>3</sup> which led to the conclusion that, a short interval after receiving an excitation, each unit of auricular tissue undergoes a brief fractionate contraction lasting about 0.06 second and then relaxes—an interpretation that has recently been confirmed by Lewis and his co-workers.<sup>4</sup> Auricular systole begins with the first fractionate contractions near the sinus node, and ends when a balance of the fractionate relaxations and contractions causes no further decrease in the length of the entire auricle. Since the fractionate units excited first begin to relax during mid-systole, the pressure in the auricles and large veins rises only during the early half and decreases during the latter half of auricular systole. We may therefore divide auricular systole into (a) a dynamic phase, during which blood is injected into the ventricles and (b) an inflow phase, during which some blood actually flows into the auricles from the central veins.

*The Consecutive Phases of the Ventricular Cycle.*—In order to interpret the dynamic mechanisms of the ventricles, it is sometimes desirable to subdivide their periods of systole and diastole into shorter phases. In doing this, synchronous pressure curves recorded by optical manometers from the cardiac chambers and aorta, together with ventricular volume curves, are of great assistance.

While it would be tedious to describe, even superficially, the apparatus and technic required for recording pressure and volume changes accurately, the principles of such apparatus can be outlined in a few words.

Suppose (Fig. 1) that small chambers, A, B and C, filled with fluid and covered by very tensely drawn rubber membranes, are inserted through the auricular and ventricular walls and into the aorta. Each membrane will then respond to every pressure variation by a microscopic movement. This can be magnified and rendered visible by reflecting a narrow band of light from a small mirror fastened to the rubber. By allowing these beams to focus on a film (D) moving in a specially constructed camera, a true picture of the pressure variations can be recorded.

In order to record the volume changes of the ventricles, they are slipped as far as their a-v junctions into a glass oncometer covered by a rubber diaphragm in which an opening, corresponding in shape and size to the a-v ring, has been cut. This oncometer is connected

3. Wiggers: *Am. J. Physiol.* **42**:133, 1916; **40**:218, 1916.

4. Lewis, Feil and Stroud: *Heart* **7**:131, 1920.

with a large recording tambour. When blood is expelled and the ventricular volume decreases, the volume of air in the tambour is reduced by a corresponding amount, and the tambour lever falls. When the volume of the ventricles, on the other hand, increases as blood flows in during diastole, the lever rises. By connecting the interior of the large tambour with an optical segment capsule, the very slight pressure variations which correspond to the volume changes may be projected and recorded optically (Henderson <sup>5</sup>; Wiggers <sup>6</sup>).

While the conformation of such volume and pressure curves alters under different experimental conditions and varies also in different

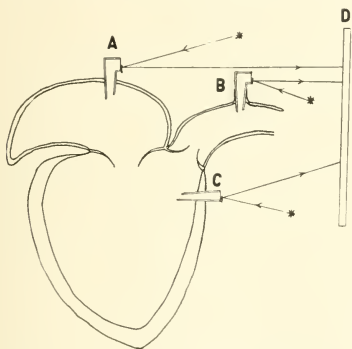


Fig. 1.—Schematic representation of principles employed to record pressure curves optically from auricles (A), ventricles (C) and aorta (B). D, sensitive photographic surface. Description in text.

animals examined, their general character and the time relations are represented fairly well by the curves shown in Figure 2. A careful study of many kilometers of such records obtained from over 200 dogs under a large variety of experimental conditions, together with a careful consideration of similar dynamic studies carried out by Garten,<sup>1</sup> Piper, Straub<sup>7</sup> and C. Tigerstedt, have led me to interpret and subdivide the ventricular cycle as follows: At the onset of ventricular systole (Fig. 2, I) the pressures within the auricle and ventricle are

5. Henderson and Collaborators: *Am. J. Physiol.* **16**:325, 1906; **23**:345, 1909.

6. Wiggers: *Circulation in Health and Disease*, 1915, Phil., Lea & Febiger.

7. Straub: *Deutsch. Arch. f. klin. Med.* **115**:531, 1914; **116**:409, 1914.

approximately equal. At this time, as indicated by the experiments of Dean,<sup>8</sup> the a-v valves are in the act of floating into apposition. As Henderson and Johnson<sup>9</sup> suggest, this movement probably is initiated by the sudden cessation of the jet when the peak of the presystolic auricular wave is reached. The first elevation of intraventricular pressure firmly closes these valves, and the ventricle then contracts in an absolutely isometric fashion. This first phase of ventricular systole,

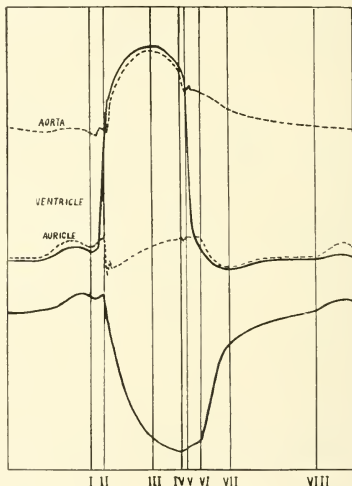


Fig. 2.—Superimposed curves of pressure changes in ventricle (heavy line), aorta (upper dotted line), and auricle (lower dotted line) together with volume changes in two ventricles (lower solid line). 1-IV, systole; IV-VIII, diastole. Detailed phases of each discussed in text.

extending from the beginning of the pressure rise (I) until the opening of the semilunar valves (II), is preferably designated as the isometric contraction phase.

As soon as intraventricular pressure exceeds intra-aortic pressure, the semilunar valves open and a comparatively large volume of blood

8. Dean: *Am. J. Physiol.* **40**:206, 1916.

9. Henderson and Johnson: *Heart* **4**:69, 1912.

per unit time is ejected. As long as the volume ejected remains greater than the outflow from the peripheral arterioles, the aortic and intraventricular pressures continue to rise. This summit (III) marks the end of a second phase of systole which I have designated as the maximum ejection phase. As soon, however, as the volume of the systolic discharge decreases to such an extent that it no longer equals the peripheral outflow, the aortic and intraventricular pressures begin to decline. This third phase (extending to IV) may be designated as a phase of reduced ejection. It terminates the period of systole.

At the onset of ventricular relaxation, aorta and ventricle are still in communication. The first event, viz., the approximation of the semilunar valves, is signaled by a sharp drop in both aortic and intraventricular pressures (IV-V), designated as the incisura. This marks a fourth or protodiastolic phase of the ventricular cycle. Following the closure of the semilunar valves (interpreted as taking place at V) and until the a-v valves have opened, the ventricle relaxes without any flow of blood either from or into its cavity. This phase (extending from V to VI) may be designated as the isometric relaxation phase. With the opening of the a-v valves (VI), a rapid ventricular inflow begins. This continues until an equalization of pressure between the auricle and ventricle has taken place (VII), or until a subsequent systole interrupts the filling. This is the sixth phase, which may be designated as the early diastolic inflow phase. In long cycles, and when auricular pressure is normal, a period of reduced filling or approximate stasis is indicated in the volume curve (VII and after), which may be designated, after Henderson's suggestion, as the phase of diastasis. Finally, there may be added an eighth phase during which the dynamic interval of auricular systole (VIII) affects the filling or pressure of the ventricles. This summary of the dynamic events occurring during ventricular systole and diastole and the suggested subdivision of the periods of systole and diastole into shorter phases is schematically indicated in Figure 3. On the diagrams are also indicated the average duration of these consecutive phases recently found in animals in which the thorax remained intact.

## II. THE LAWS GOVERNING CARDIAC BEHAVIOR UNDER NORMAL AND ABNORMAL CONDITIONS

Under a variety of physiologic, pharmacodynamic and pathologic conditions, the heart must adapt itself to an altered venous return and changes in arterial resistance. In association with or quite independent of these, changes in rate and rhythm may take place. Again, the inherent functions of cardiac irritability and contractibility may be stimulated or depressed.

When such a combination of influences unite to modify the cardiac mechanisms, it may become quite perplexing, if not hopeless, to analyze the factors responsible for the resulting cardiac behavior. It is quite probable that this accounts for the facts (1) that "clinical hearts" do not always seem to conform to the laws and reactions established by laboratory experiments, and (2) that they do not always react to drugs as do the hearts of experimental animals.

It is important, therefore, that the laboratory investigations concern themselves primarily with the alteration produced in cardiac behavior when, as nearly as possible, only one of these variable influences operates at a time. The history of such researches has been the history of all investigations involving the use of complicated apparatus to

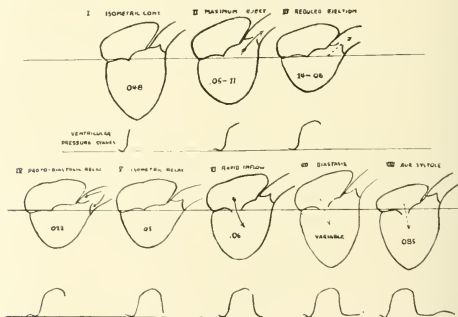


Fig. 3.—Series of pictorials illustrating the consecutive phases of the cardiac cycle established from pressure and volume curves. The extent of the ventricular pressure variations that have been completed at the end of each phase are also indicated. Upper series, phases of systole; lower series, phases of diastole.

unravel the mysteries of complex functions. One investigator demonstrates a series of striking facts; their uniformity suggests that they are grounded on a common factor or principle; a theory or law of cardiac behavior is formulated. Another investigator discovers certain facts which it is difficult or quite impossible to harmonize with such a conception. The older law is apt to be considered disproven and a new one is formulated. Rebuttal and counterchanges supported by new and still newer experimental facts fill many pages of scientific literature until he who follows every development cannot always decide what to believe either in his own work or in the experiments of others.

With the many differences of opinion regarding the fundamental laws controlling the functions of the heart beat, it is possible to keep from falling into this hopeless mental state only by bearing in mind that the disapproval of certain interpretations does not necessitate the discard of all experimental facts arrayed in its support. On the other hand, an investigator may have established a broad principle and yet have failed to realize the limitation of its applicability. We must admit, I believe, that while each new series of experiments has contributed its building stone, there still remains to be hewn out of unknown facts the keystone to that group of laws which regulates the heart beat under diverse conditions of circulation.

*The Heart Rate as a Factor in Controlling Cardiac Efficiency and the Law of Uniformity of Behavior.*—In a large series of experiments, Henderson and his co-workers<sup>5</sup> have contributed greatly to our understanding of the cardiac mechanism. They have demonstrated by experiments, that to me seem not to be negated by apparently contradictory results of other investigators, that the ventricular filling occurs chiefly during the earlier portion of diastole, and that, in slowly beating hearts, there exists a phase of diastasis during which a very gradual filling of the ventricle takes place. They have done much toward demonstrating that the blood volume received by the ventricle during diastole also determines the amount discharged during systole. They have analyzed how variations in ventricular tonus can modify both filling and systolic discharge. They have demonstrated how, as the heart accelerates and the cycle shortens, the succeeding diastolic filling is encroached on more and more until the diastolic inflow is abbreviated and systolic discharge is greatly affected. That this tendency of the systolic filling to be decreased as the heart accelerates is one of the fundamental compensatory mechanisms which prevents an excessive minute volume from being discharged during rapid heart action, cannot be questioned. Henderson and his collaborators maintain further, however, that both under normal conditions of venous return as well as during states of increased venous pressure, the systolic discharge cannot be further affected by the venous pressure change or volume of venous return, but hold that it is determined solely by the duration of the cardiac diastole. They found that the volume curves of the ventricles, at any heart rate, are practically superimposable on portions of a standard curve obtained during a slow beat. This led them to formulate the "law of uniformity of cardiac behavior," according to which the systolic volume discharged is entirely a function of heart rate as long as the venous pressure is at or above normal.

The strict operation of this law has been questioned by subsequent investigators because it does not appear to square with other experi-



mental evidence. In 1914, I<sup>10</sup> found that systolic and diastolic blood pressures in man vary, independently of heart rate, which was interpreted to indicate that the rate of ventricular filling in man must alter during normal inspiration and expiration. Henderson and Haggard<sup>11</sup> have subsequently attempted to nullify these experiments by showing that systolic and diastolic pressures, measured by the sphygmomanometer method in man, failed to increase when a person is tilted on a board from a horizontal to a head-down position—a procedure obviously increasing the venous return and auricular pressure. Such experiments cannot be regarded as crucial, however, for, even if it admitted that the ordinary methods of estimating human blood pressure are sufficiently delicate to detect small variations, the fact that their experiments were always attended by heart rate changes, make it quite impossible to lend much significance to the pulse pressure change that occurred. On the basis of subsequent work, I am quite ready to admit, however, that my interpretation of pulse pressure changes during inspiration and expiration are more probably explained by a direct effect of the changing negative pressure on the aorta itself.

The view that the systolic discharge is unable to vary independently of heart rate when venous pressure is increased has been disputed by the results of Krogh,<sup>12</sup> Plesh<sup>13</sup> and Zuntz,<sup>14</sup> for it is difficult to explain the greatly augmented blood flow through the lungs during exercise in any other way than by assuming that the systolic discharge increases above normal even when the heart is very rapid. Krogh endeavored to show, furthermore, that such results may be harmonized with Henderson's volume curves if one of two assumptions is made, namely, either that the venous supply is normally inadequate, or that some myocardial factor increases the vigor of systole. Henderson and Barringer<sup>15</sup> again investigated the question as to whether the accelerator nerves can affect the amplitude of systolic discharge independent of rate—with negative results. Subsequently, Starling and his collaborators<sup>16</sup> re-investigated the subject by means of their "heart-lung preparation" and concluded that the ventricular volume curves are not superimposable. Their volume curves indicated to them that when venous pres-

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10. Wiggers: *J. Exper. M.*, **19**:1, 1914.

11. Henderson and Haggard: *J. Pharmacol. & Exper. Therap.*, **11**:189, 1918.

12. Krogh: *Skand. Arch. Physiol.*, **27**:126, 1912.

13. Plesh: *Centralbl. f. Physiol.*, **26**:90, 1912.

14. Zuntz: *Ztschr. f. klin. med.*, **74**:347, 1912.

15. Henderson and Barringer: *Am. J. Physiol.*, **31**:228, 352, 1913.

16. Starling and Collaborators: *J. Physiol.*, **44**:206, 1912; **47**:275, 286, 1913; 348, 357, 465, 1914.

sure increases above normal, the systolic stroke is greatly increased without any change in heart rate. Similar conclusions have also been reached by Straug<sup>7</sup> and Socin.<sup>17</sup>

We may inquire what changes must necessarily take place if the systolic discharge increases at the same time that the heart accelerates. Obviously, such a condition is made possible only by an increase in the expulsion rate or by a lengthening of the ejection phase. Recent experiments in which I measured the duration of systole after saline infusion indicate that this causes a definite prolongation of the ejection phase, quite independent of diastole length.

On the basis of recent experimental work, Katz and I<sup>18</sup> have found it necessary to conclude also that, even under quite normal conditions, the systolic discharge of the heart may not be regulated by changes in the duration of cycle alone. Our evidence is based on the following considerations: Although emphasis has not been laid specifically on the fact by Henderson and his co-workers, it is evidently a corollary of the "uniformity of behavior law" that the duration of systole is fixedly related to cycle lengths under all conditions which normally produce a change in heart rate. As the cycle shortens from a very long to a very short cycle, the phase of systolic ejection must, at first, be very little affected but becomes progressively shorter. By determining the theoretic systole and cycle lengths and expressing this as a systole: cycle ratio, it was found possible to construct a curve of theoretical  $s/c$  ratios. To this curve, the actual  $s/c$  ratios at different heart rates should conform if the law of superimposability holds good. It was found, however, that, while the actual  $s/c$  ratios obtained during normal rates and during vagus beats coincided reasonably well, the ratios were very much below this curve when the heart rate increased during stimulation of the accelerator nerve.

In carrying this work still further, Katz and I, working independently and by different methods, have obtained other evidence which indicates that during vagus slowing the periods of systole and diastole are also not strictly related to the length of previous diastole. When, for example, the peripheral end of a vagus nerve is stimulated with a current producing moderate slowing, systole increases in length for several succeeding beats, becoming stationary only when a new equilibrium has been established. This occurs regardless of previous diastole lengths and often contrary to them. After reflex slowing induced by central vagus stimulation, the duration of systole in a few experiments was longer than in peripheral vagus stimulation, even though a much greater slowing was produced by previous peripheral stimulation.

17. Socin: Arch. f. d. ges. Physiol. **160**:132, 1914.

18. Wiggers and Katz: Am. J. Physiol. **53**:49, 1920.

When partial asphyxia produces cardiac slowing, the periods of systole may remain unchanged or even become abbreviated.

Such results indicate that while a constant relation between systole and diastole lengths, such as complete superimposability of beats demands, approximately obtains when a stable equilibrium has once been produced after direct vagus stimulation, there are other factors at work which more than counterbalance such a control of systole length.

On the basis of all these investigations, we must conclude that, while the systolic discharge is mechanically determined by the heart rate when other factors are unchanged, the simultaneous variations of these factors even under normal conditions prevent the beats from being superimposable.

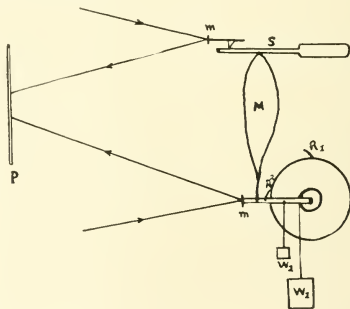


Fig. 4.—Diagram showing arrangement of muscle activating a work adder, with attachments for photographically recording tension changes and length changes, optically. S, spring; m, small mirrors reflecting light beam to photographic film; P. Further description in text.

*The Response of the Heart to Changes in Venous Return and Arterial Resistance.*—The response of the normal heart to changes in venous return and alterations in arterial resistance have been studied by recording both the volume curves of the two ventricles, and the pressure curves from the separate ventricles. While such methods have their difficulties and drawbacks, their use has served to advance our understanding of an important phase of cardiodynamics. In order to grasp the significance of such investigations in their fullest, however, it is necessary to recall the nature of the contraction processes in a skeletal muscle which operates in a manner similar to the heart.

It has been pointed out by Henderson that, with certain reservations, the heart contracts as a skeletal muscle operating a work-adder. In such an arrangement (Fig. 4) the weight ( $W_1$ ) which the muscle is required to lift is supported by the ratchet ( $R_1$ ) and, consequently, weights the muscle only during contraction. During the rest period, as well as during the process of relaxation, the muscle is stretched by a smaller weight  $W_2$ . Obviously, the greater this weight becomes, the greater the length of the resting muscle. This resting length of the muscle is referred to as its initial length. When this weight increases, the muscle fibers are not only lengthened more but are also placed under a greater tension, referred to as its initial tension. Changes in this initial tension may be recorded graphically and evaluated by attaching the upper end of the muscle to a stiff spring, the very slight movements of which can be greatly magnified and projected (Fig. 4). A muscle so arranged is said to be "after-loaded." Before it can shorten its tension must be increased sufficiently to overcome the load  $W_1$ , i. e., it first contracts isometrically. Such a tension variation will be recorded by the upper lever a short interval before the lower lever begins to register a decrease in length. This accomplished, the ratchet  $R_2$  engages and the weight is raised during the remainder of the contraction phase. Inasmuch as the tension during this phase of contraction does not alter appreciably, it is said to contract in an isotonic manner. At the onset of relaxation, the ratchet lever  $R_1$  engages and the relaxation process is assisted by the small weight  $W_2$ .

In the normally beating heart, the venous pressure represents the distending load ( $W_2$ ) and determines the initial tension as well as the initial length of the ventricular muscle fibers, while the arterial pressure corresponds to the lifted load ( $W_1$ ). It is clear, therefore, that changes in initial tension as well as the tension changes during contraction and relaxation may be conveniently followed by recording optically the intraventricular pressures. Changes in the length of the muscle fibers, as Frank, Paterson, Piper and Starling and others have pointed out, may be evaluated most satisfactorily by studying the changes in the ventricular volume during consecutive phases of the heart cycle.

In 1914, I reported<sup>6</sup> experiments which seemed to demonstrate that every increase or decrease in the volume of blood returning to the right auricle affects simultaneously the initial tension, height, and contour of the right intraventricular curve. These experiments were the first to demonstrate that the laws derived by Frank from a study of the frog's heart apply also to the naturally contracting mammalian ventricle. In brief, the conclusion seemed justified that *the gradient of the isometric pressure rise as well as the systolic pressure-maximum are determined by the initial tension* as long as marked changes in

arterial resistance or alterations in the inherent contractility of the heart are not produced. At the same time, it was shown that any increase in pulmonary arterial resistance is also capable of altering the pressure-maximum in the right ventricle under conditions of unchanged venous inflow. Finally, it was pointed out that independent of, or coincident with, these factors the pressure-maximum may be determined by the inherent contractility or irritability of the heart itself.

Shortly after the publication of this work, a series of investigations were published which apparently analyzed the reactions of the heart to increased venous return and increased arterial resistance in a much more fundamental manner. This was accomplished by limiting the circulation to the heart and lungs and controlling independently the venous inflow and the arterial resistance. With such a "heart-lung" preparation dynamic experiments were carried out in London, by Starling,<sup>16</sup> working at various times in association with Knowlton, Mark-

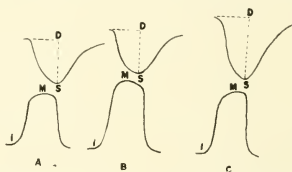


Fig. 5.—Diagrammatic representation of ventricular volumes (upper curves) and pressure changes in left ventricle (lower curves), according to results of Patterson, Piper and Starling. D, diastolic volume; S, systolic volume; D-S, systolic discharge; I, initial pressure; M, pressure-maximum. A, normal controls; B, after increased arterial resistance—initial pressure (I) unchanged, initial volume (D) increased, pressure-maximum (M) higher, systolic discharge (D-S) unaltered. C, after increased venous inflow—initial pressure (I) decreased, initial diastolic volume (D) increased, systolic discharge (D-S) and pressure-maximum (M) increased.

walder, Patterson and Piper, and contemporaneously by Straub<sup>7</sup> in Munich. Subsequently, Gesell<sup>19</sup> in this country, has also utilized a similar method of experimentation.

The first investigations of Starling and his associates showed that the systolic discharge of the ventricle at any constant rate is unaltered by very considerable change in arterial resistance as long as the inflow is kept constant. On the other hand, they found that, within wide limits, the heart is able to increase its output in direct proportion to the venous inflow. Similar results were obtained by Socin<sup>7</sup> and de Heer.<sup>20</sup>

19. Gesell: *Am. J. Physiol.* **39**:239, 1916; **40**:267, 1916.

20. de Heer: *Arch. f. d. ges. Physiol.* **148**:45, 1912.

In studying the cardiac reactions more in detail, Patterson, Piper and Starling obtained results which are diagrammatically illustrated in Figure 5. Their records show that when the venous inflow increases, the ventricles are more distended in diastole and the systolic discharge increases (Fig. 5, A and C). The initial tension in the left ventricle, however, may not increase, but, on the contrary, may actually be lower. Nevertheless, the intraventricular pressure-maximum appears to rise.

When arterial resistance alone was raised, they again found an increased diastolic volume due to a retention of blood during the first few beats. Their tracing indicates that once dilated to a stable capacity, the heart expels at least as large a systolic volume as before the increase in resistance (Fig. 5, A, B). In studying the intraventricular pressure changes accompanying such reactions, it was also found that the left intraventricular pressure-maximum increases, that the pressure

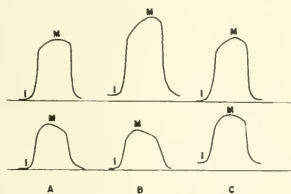


Fig. 6.—Diagrammatic representation of pressure changes in right (lower) and left (upper) ventricles according to Straub's results. A, normal control curves; B, after increased arterial resistance—initial pressure (I) increased in left ventricle, unaltered in right, pressure-maximum (M) higher in left ventricle, lower in the right. C, after increased venous inflow—initial pressure (I) increased in right but not in left ventricle, pressure-maximum (M) increased markedly in right and very slightly in left ventricle.

gradient rises steeper and that the duration of the period of systole is increased. In some cases, however, the noteworthy observation was made that the initial tension is scarcely affected in the left ventricle. These results, together with observations on the isometric contraction curves obtained from the terrapin heart, led them to conclude that, "in the reaction of the heart to increased venous inflow and increased resistance, the only factor which constantly varies with the response of the ventricles is the volume of the heart, i. e., the length of its muscle fibers." They believe, on the basis of such experiments, that we are justified in ascribing the increased energy of the cardiac contractions under conditions of increased inflow or augmented resistance entirely

to alterations in the length of the muscle fibers and not to change in tension on the fibers, which, as they interpret it, may or may not be present at the same time.

The contemporaneous experiments of Straub<sup>7</sup> led on the whole to similar, yet in some vital respects, different conclusions. He also found that, under a constant venous inflow, increased arterial resistance leads to a systolic retention resulting both in systolic and diastolic distention. The systolic discharge remained unaffected. His optical pressure curves indicated, moreover, that, in the left ventricle, not only the maximum pressure, but also, the initial pressure increases (Fig. 6, cf A and B). Such results, contrary to those reported by Starling and his co-workers, would indicate that an increased pressure-maximum is constantly associated with, if not fundamentally due to, an increased initial pressure. In the right ventricle, however, he found no increase in height nor elevation of the initial tension; in fact, in some cases, the pressure-maximum seemed to be reduced. These results, it will be recalled, are quite contrary to those previously reported by Fühner and Starling<sup>16</sup> who found that a "backing up" of blood always occurs when the left heart works against an increased resistance. In attempting to harmonize these discrepancies, Straub pointed out that he also was able to obtain such "back pressure" effects when the arterial pressure at the start was low and the coronary supply therefore insufficient to maintain the heart in prime condition. Straub considered the latter reaction as one of a hypodynamic and uncompensating heart; Fühner and Starling considered it the reaction of a normal heart. We shall revert to a discussion of this question later. When the inflow rate was increased but the arterial resistance kept constant, Straub found, similar to Starling and his co-workers, that the two ventricles dilate somewhat and expel larger systolic volumes. The intraventricular pressure curves taken from the two ventricles again showed differences (Fig. 6, A and C). In the right ventricle, changes similar to those reported by myself were constantly observed, i. e., increased diastolic filling always occasions an increased initial tension and a higher pressure-maximum. In the left ventricle and in confirmation of Starling's results, no changes in initial tension occur although the pressure curves did become somewhat higher. According to these results, the increased discharge of the right ventricle is unable to affect the diastolic filling of the left sufficiently to cause an elevation of initial tension. While Straub interprets his results as indicating that initial tension is the primary factor in determining ventricular efficiency, the increased systolic discharge of the left ventricle must, in such cases, be assigned to changes in initial length or initial volume rather than initial tension.

In investigating the importance of auricular systole in the dynamics of the ventricle, Gesell,<sup>19</sup> was compelled to consider the broader question as to whether initial length or initial tension primarily determine ventricular efficiency. In the auricle of the river turtle, which shows rhythmic fluctuations in tonus, he found it possible to study the effect of changes in tension and length independently. His results indicated that in the auricle of the turtle, increased strength of contraction may accompany either increased length of fiber while initial tension remains constant, or increased tension while initial length remains the same. Further experiments on a mammalian heart-lung preparation led him to conclude that this also applies to the mammalian ventricles. The latter experiments may not be regarded as quite conclusive, however, because the method employed to record variations in tension and length do not appear to be quite adequate for the study of the mammalian circulation. As a result of his work, Gesell suggests that, while both initial length and initial tension may determine ventricular efficiency, the surface-volume relations are also concerned.

With these conflicting views before us it seems desirable to re-investigate whether measurable differences of initial tension fail to accompany such experimental procedures as have been definitely shown to increase initial volume. This, I have recently attempted in intact animals. At once we may anticipate the loud objections that experiments carried out on intact animals can, of course, not prove valid either the one contention or the other.

Extensive experience has convinced me that it is not so difficult to control or evaluate the separate factors in intact circulation experiments as has been claimed. If the vagi nerves have previously been severed, variations in heart rate are no more extensive than those which occur in perfused hearts. The venous return may readily be reduced by compression of the vena cava and increased by the injection of innocuous normal saline. In neither event is arterial resistance altered appreciably. Increased resistance may be induced either peripherally by vasoconstriction or more centrally by mechanical compression of the aorta. If carried out for intervals which are short but quite long enough to obtain observations, the venous return is either not sufficiently affected or, if modified, can be evaluated in interpreting the reactions.

Are the experimental conditions in the heart-lung preparation better or more controllable? The very fact for which these experiments are lauded, viz., that each factor—venous inflow, arterial resistance and rate—may be controlled at will, makes them a source of trouble. In such schemes, it is the first duty of the experimenter so to adjust the artificial factors (the controllable factors) that the heart beats after a fashion which he interprets as normal. What criterion other than instinct can



guide him? We have already pointed out that the adjustment of the artificial resistance to the inflow volume apparently determines whether or not a "back pressure" effect takes place on raising the arterial resistance. Each experimenter will be ready to admit that his adjustment approximates normal. Fühner and Starling find "back pressure effects" as far back as the right auricle on increasing artificial resistance; Straub finds that the pressure in the right ventricle decreases. Both results can not apply to the intact normal circulation. Who shall judge between them? I have been able to show in similar heart preparations that, with constant arterial resistance, an increased systolic discharge may cause either an increased or decreased pulse pressure in the arteries, depending on whether the arterial resistance during the so-called "normal" is relatively great or small, as compared with the venous inflow. Both reactions cannot be characteristic of the intact circulation. The fact that mean arterial pressure approximates the normal found in animals of course means nothing whatsoever. In short, I believe that in many instances it is possible to set the "normal" so that absolutely diverse propositions may be clearly (!) demonstrated with equal facility.

Aside from the judgment of the experimenter, we have possible alterations in the physiological condition of the perfused heart to deal with. Does it react as the heart in the intact circulation? Always, it is separated from all nerve control—not without its effects on the duration and strength of ventricular contraction. Usually, also, the pericardium is opened—causing, as has been shown in Starling's own laboratory by Kuno, important changes in the distention of the ventricles. Commonly also, the capacity of the rubber tube substituted for the aorta is too small to accommodate, in a natural manner, the ejected blood, so that the entire systolic volume must each time be forced through a small cannula tied into the narrow lumen of the innominate artery. In the heart-lung preparation, the blood supply of the heart also changes in a manner which is quite abnormal, whenever the resistance increases. If the aortic resistance increases in the natural circulation, short circuits are always available through which an excess of blood may flow. In the heart-lung preparation the only short circuit is the coronary system which then apparently allows exorbitant volumes of fluid to flow through it. A few direct observations may be interesting: If we use the figures of Patterson, Piper and Starling, we can only conclude that normally from 25 to 35 per cent. of the entire systolic discharge passes through the coronary system, a volume which if correct represents a most abnormal state of the coronary circulation which certainly does not conform to the intact heart. Straub found that after compression of the aorta, the coronary blood flow increases

so greatly that right auricular pressure is thereby augmented—a condition just the reverse of that obtaining in the intact circulation. Frequently also, the heart is supplied with a blood-saline mixture of unnatural composition. In Straub's experiments, for example, the deficiency of carbon dioxid in the blood, according to his own interpretation, caused the hearts to beat at the excessive rate of 300 per minute. Finally, it seems very doubtful whether the preparation accomplishes the task for which it is specifically employed. I question, for example, whether it is possible to alter any one factor—e. g.,—heart rate, venous pressure or arterial resistance—without at the same time affecting some other factor. Thus, it appears both from the records of Patterson, Piper and Starling and those of Straub that, whenever the arterial resistance increases considerably, the filling pressure in the right auricle also augments. Again, I have found it exceedingly difficult in similar experiments to dissociate changes in temperature from changes in venous inflow; the two seem intimately interdependent. Whenever the inflow rate is increased, a tendency exists to increase the temperature of the heart muscle; when it is reduced, the reverse tendency exists. The temperature change may be only 0.5 C.; but what changes in inherent irritability and contractibility may not this induce! How can the influence of this factor be separated from that produced by augmented inflow itself? On the whole, who dares to say that the heart in such preparations reacts as would an intact heart or that every factor can be perfectly controlled?

I cite these objections not to condemn the method, nor to discourage its employment in the analysis of the cardiac mechanisms. On the contrary, I am of the opinion that its employment has greatly enhanced our knowledge of the fundamental laws according to which the heart *can* react. I merely wish to emphasize the possibility that such laws may apply only to special conditions and must always be transferred to the intact circulation with the greatest reserve and caution.

With such reflections in mind, I have recently investigated the ventricular pressure and volume changes during conditions of altered arterial resistance and venous inflow on intact animals, for, in such experiments, in contrast to studies on the heart-lung preparation, it is possible to study what probably *does* happen when the heart reacts to different influences. Both right and left intraventricular pressures were simultaneously recorded by optical manometers. In some experiments the volume changes were also recorded; in others, volume curves were omitted in order to test the same procedures in animals in which the natural pericardial support of the ventricles was maintained.

In seventeen experiments, so far completed, it was found, without exception, that any sudden increase in venous return which increases

also the volumes of the ventricles, always promptly elevates the initial tension and pressure-maximum in the right as well as left ventricle. This is illustrated by the records shown in Figure 7, II. Curves "1" are normal controls. Fifty c.c. of warm saline solution was then allowed to flow into the external jugular vein in twelve seconds. In

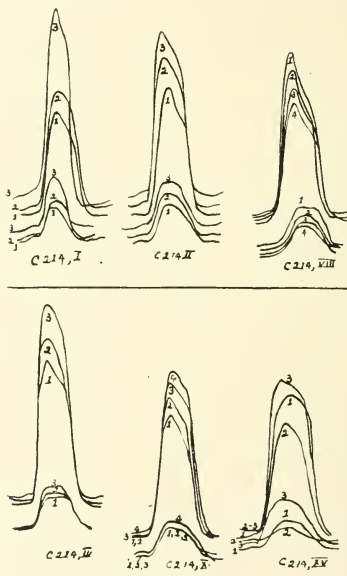


Fig. 7.—Superimposed tracings of right (lower) and left (upper) intraventricular pressure curves, after experiments of author. 1, normal as compared with effects during asphyxia; II, normal as compared with saline infusion effects; VIII, normal as compared with decreased venous return after vena cava compression; IV, normal as compared with effects of vaso-constriction; X, as compared with effects of aortic compression; XV, normal as compared with effects of chloral (2) and strophanthin (3).

other experiments, this had been shown to definitely increase the diastolic volume of the ventricles and augment the systolic discharge in

from 2 to 3 seconds. Four seconds after, curves "2" were recorded. Both intraventricular pressure curves show an elevation of initial, as well as maximum pressure. Toward the end of the infusion, the third series of curves were taken; a further elevation of initial and maximum pressures in both ventricles is obvious.

Reduction of the venous inflow produced by clamping the inferior vena cava has precisely the reverse effects on initial and maximum pressure in the two ventricles. This is shown in records labeled as observation VIII. Such changes in initial pressure occur with great promptness when the volume of fluid returned is either decreased or increased. Thus, in observation VIII, "1" shows the normal control, "2," "3" and "4" illustrate the changes taking place during the second, fourth or sixth beats after compression of the vena cava.

When arterial resistance increases either through intense vasoconstriction or mechanical compression of the aorta, the initial pressure is always elevated when it is of sufficient degree to cause a dilation of the ventricles. The details of these changes are illustrated in the series of records shown in IV and X. Observation IV indicates the final results during intense vaso constriction reflexly induced by stimulating the central end of a divided vagus nerve. Curves "1" are normal controls. While arterial pressure (recorded supplementary) was on the ascent, curves "2" were recorded. At the height of the pressure reaction, curves "3" were taken. In both, a considerable elevation of initial pressure is indicated in the left ventricle pressure curves and a relatively smaller increase is discernible in the right ventricle. In observation X are noted the immediate effects of raising the arterial resistance through mechanical compression of the thoracic aorta. Curves "1" are normal, curves "2" represent the pressure changes during the first beat following compression. The pressures in the right ventricle are unaffected. The pressure-maximum increased by virtue of the higher resistance and pressure existing during the contraction process. The initial pressure has not elevated. Curves "3" show the changes in the third beat after compression. Increased initial tension and pressure-maximum occur in the left ventricle, the pressure in the right still remaining unchanged. Curves "4" represent the fifth beat after compression. Initial pressure and pressure-maximum are further elevated in the left and, for the first time, in the right ventricle also.

Experiments of another order have also been carried out. In these, the ventricular volume curves were recorded on a slowly moving smoked paper; the two intraventricular pressure curves, as before, at the first indication of an increase in diastolic volume (initial length) after slow saline infusion, optical pressure curves were at once recorded.

Comparison with normal curves showed that the initial pressure increase in the right ventricle was never dissociated from an alteration in initial diastolic volume.

This state of affairs obviously holds good only as long as the inherent functions of the cardiac muscle are not excited or depressed. There are many evidences of deviations from this rule; both in the literature emanating from other laboratories and my own. Thus, when the initial pressure becomes elevated to an excessive degree, the intraventricular pressure-maximum no longer increases but becomes lower at the same time that the systolic discharge lessens. So also, when the heart is long distended by a great inflow or is required to react against a very high arterial resistance for a long time its subsequent power of response is reduced. The irritability of the heart may also be depressed or stimulated by chemical agents, in which case the pressure-maximum and systolic discharge are not related to the initial pressure. This is illustrated in observation XV, in which curves "1" again show normal controls. Curves "2" are representatives of pressure changes following the use of chloral hydrate. Initial pressure is greatly elevated in the right, very slightly in the left ventricle. In spite of this, the pressure-maximum is lower in both ventricles. The heart was obviously dilated. Neither increased initial pressure nor increased initial length determines the vigor of the ventricle when the myocardium is depressed. Curves "3" were obtained after subsequent use of strophanthin. The tension maximum increased above normal in both ventricles—the initial tension remaining unaltered in the left and decreased in the right.

Viewing all the experimental evidence in the light of the more fundamental work of Blix, Hill and others on skeletal muscle, we must be ready to admit that the dynamic efficiency of the ventricle may be fundamentally determined by such factors as initial length, and diastolic surface-volume relations. It is not so evident, however, (except, perhaps, under conditions of very small venous inflow, or where the ventricle has lost its tonus completely) how any increase in diastolic volume (and initial length) can take place otherwise than by the force of an increased initial tension. The ventricles are filled to capacity even under very low auricular pressures. It would seem that any additional increase in volume must necessitate a stretching of the elastic and tonic walls of the ventricle. This requires an increased auricular and increased initial pressure. The pressure required to stretch the walls sufficiently to admit a definite volume increase need not be great, if the tonus is low; but must be considerable, if it is high. The pressure increase is not proportional to the volume increase; but an increase must exist. We may reiterate: While initial length of

ventricular fibers and diastolic surface-volume relations may fundamentally determine myocardial efficiency, it is difficult to picture how these factors can be increased except through an increase in initial tension.

### III. THE DYNAMICS OF THE CIRCULATION IN HEART DISEASE

The signs and symptoms arising from acute or chronic cardiac disease are the expressions of dynamic consequences which occur when the normal valvular mechanism is impaired or the functional capacity of the ventricular myocardium is affected. As the latter are always concerned more or less in valvular effects, it seems desirable to analyze, on the basis of experimental results, how the myocardium becomes abnormal in its function, to consider the factors of safety that are at once called into play, to analyze how additional compensatory mechanisms gradually develop, and finally, to attempt an answer as to why these mechanisms ultimately fail to accomplish the task for which they were developed.

*The Hypodynamic or Inherently Weakened Heart.*—Under this heading I mean to catalogue cardiac conditions in which the working capacity of the ventricles has been reduced. It is, I believe, the condition which so frequently follows or terminates severe febrile or infectious processes. Clinically, it is recognized chiefly by the feeble heart sounds (particularly the first) and the small pulse amplitude. The latter has definitely been proven to be caused by the decreased systolic discharge; the enfeeblement of the first sound I<sup>21</sup> have recently shown to be related to and diagnostic of a reduction in intraventricular tension.

It is probable, therefore, that we have, in this hypodynamic heart of the clinic, a condition not unlike that produced by depressant drugs such as chloral, chloroform, etc., and consequently, we may venture an interpretation of the cardiodynamics on the basis of experimental results obtained from the use of such drugs.

The capacity of the ventricle for work is, of course, a function both of pressure and volume, as well as time. O. Frank has expressed it by the integral,  $A = \int_{T_0}^{T_1} P \cdot V \cdot dx$  in which  $A$  represents the work;  $P$ , pressure;  $V$ , volume;  $T_0$ , time of opening of semilunar valves;  $T_1$ , the time of closure of the semilunars. Owing to the facts that the volume curves of each ventricle cannot be separately recorded and that initial tension is a function both of aortic resistance and venous filling, it has not been found possible to apply this formula in estimating the working capacity of the mammalian heart beating under different

21. Wiggers: Arch. Int. Med. **24**:471, Sept., 1919.

conditions. A separate study of the changes in the volume and pressure curves of the ventricles has given us, however, a clue to the essential changes taking place in the hypodynamic heart. Socin,<sup>17</sup> who studied the volume changes, systolic discharge and minute volume of the heart depressed by chloroform, found that such depression expresses itself primarily by a decreased systolic discharge and, in consequence of the inefficient discharge, by a dilation. The depressed heart retains only to a lesser degree its power of responding to changes in venous inflow or arterial resistance. If, for example, the arterial resistance is increased, the systolic discharge is not maintained as in the normal heart but continues reduced for a long time. This leads to dilation. Again, when the venous pressure is increased, it does not respond with an increased output as the normal heart, but the discharge remains unaffected.

Similar evidences of its inability to respond to increased requirements are shown by studies of the pressure curves. Experiments, not yet completed but well under way, point to the conclusion that, when the heart is acutely depressed by such agents as chloroform, chloral, alcohol, etc., the intraventricular pressure progressively rises less abruptly and to a lower level in spite of the fact that the initial pressure is elevated and the diastolic ventricular volume, to judge from volume curves, is actually greater.

The heart gradually recovers from such effects. This, we are accustomed to attribute to the fact that the chemical action gradually wears off. Pressure curves indicate, however, that this "wearing off" effect is not entirely due to the cessation of a toxic action but involves rather a process of compensation. This seems to occur as follows: As a small quantity of blood is retained during successive systoles, the initial tension and initial distention of the ventricles is greater. When this has gone sufficiently far, the hypodynamic heart reacts to the higher initial tension and the amplitude of the pressure curve again increases. In these depressed hearts, the impression is clearly gained that initial tension fundamentally determines the pressure relations; and present one instance as to why the analysis of the relative importance of initial length, and initial tension, in determining cardiac efficiency is of more than academic interest.

If cardiac depression is more severe, the ventricular pressure is not elevated to normal even if the initial pressure itself is considerably higher. By virtue of the higher initial pressure, the ventricle dilates more and more and the pressures in the left auricle and entire pulmonary circulation have a tendency to become elevated. Marked pulmonary congestion is probably avoided because the output of the

depressed right ventricle is diminished by an amount nearly equal to that of the left. Stagnation of blood in the veins and liver without pulmonary congestion can thus be explained in a logical manner.

If the influences depressing the contractile power of the ventricles are removed, or if they are neutralized by suitable cardiac stimulation, gradual recovery may take place. Such experiments favor the use of such stimulating drugs as digitalis and strophanthin in purely myocardial types of depression.

*Cardiac Strain and Fatigue.*—Cardiac strain begins when the normal or hypodynamic heart is required to eject its blood against a greater arterial resistance, or, what amounts to the same thing, a higher diastolic pressure. The reactions correspond to those previously analyzed when the arterial resistance is increased experimentally. As a result of the greater load, a small increment of blood remains behind, at once distending the ventricle. As long as the elastic and tonic resistance of the myocardium is not impaired, however, it at once elevates the initial tension. This safety mechanism causes a larger pressure elevation and a restoration of the discharge to normal. The earlier phases of this reaction are undoubtedly beneficial. With the higher pressure developed during the isometric phase goes an intensification of the first sound; and with the closure of the semilunar valves at a higher diastolic level, we get, as has been experimentally demonstrated, an accentuated second sound. As long, therefore, as both sounds remain intensified, the heart is responding by adequate safety mechanisms.

If the factors increasing diastolic pressure operate too rapidly, or if the elevation is continued too long, a second phase of cardiac strain develops. During this stage, as Bruns<sup>22</sup> has shown in the frog's heart, the inherent contractility suffers. In the mammalian hearts, the intraventricular pressure curves do not mount so high and the isometric slope becomes more gradual, even though there is a progressive dilatation of the ventricle and an increased initial pressure. When this occurs, the second sounds may remain intensified, while the first sound vibrations become reduced in amplitude. Since the tonic contraction of the cardiac muscle and its elastic resistance is unable for long periods of time to resist the gradually increasing strain, the heart begins to weaken and finally gives way (Bruns). The ventricle then dilates enormously. This marks the onset of cardiac fatigue. Straub's experiments indicate that when this occurs the pressures in the left auricle become greatly elevated and the lungs markedly distended. The right ventricle, in consequence, is compelled to contract against a greater load; it then passes through the same phases of cardiac strain as the left. During the time that dilation of the left ventricle is backing blood into the pul-

22. Bruns: Deutsch. Arch. f. klin. Med. **113**:179, 1913.



monary circuit, the efficiently contracting right ventricle adds normal volumes of blood to the pulmonary side, consequently, pulmonary congestion cannot fail to supervene during the second stage of cardiac strain, while there may be no evidence of venous congestion.

Either one of two sequels must follow: the right ventricle may pass to the stage of dilation causing the venous pressure to rise and pulmonary pressure to fall, or new compensatory mechanisms may come into play which help to reestablish normal relations.

*Tonus and Dilatation.*—These terms are constantly employed by physiologists and clinicians alike, without always a clear conception of what they really imply. When the exposed heart appears large and distended during diastole, we speak of a dilated heart or one having a low tonus. If, on the other hand, the diastolic volume is small, we are apt to speak of tonus as being high. As Patterson, Piper and Starling point out, the state of distention and tone are not necessarily related "for the volume may be merely determined by the amount of

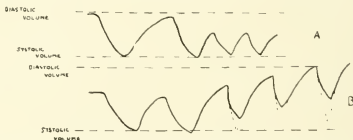


Fig. 8.—A, upper curves, series of diagrammatic volume curves showing mechanical decrease in diastolic volume when the heart accelerates, according to conceptions of Henderson. B, lower curve showing effect of increasing diastolic volume due to increased venous inflow when tonus remains normal (dotted lines) and when it is reduced (solid lines). Result, is a larger systolic volume in the former, and unaltered discharge in the latter instance.

blood entering from the veins." Henderson has shown that the diastolic volume of a heart distended by high venous inflow is necessarily greater than that of a heart which receives only a small venous inflow. Obviously, the diastolic volume of the heart is usually passively determined and in such cases the more dilated hearts are the more efficient; both because the initial and maximum intraventricular pressures are higher, and because the systolic discharge is greater (Fig. 8, A). For the sake of differentiating, let us speak of this as a physiologic dilatation (tonogenic dilatation of Moritz).

Clinically, the term "dilatation" is applied to a condition in which the heart is dilated during diastole while the systolic discharge is diminished; or, perhaps, more precisely stated, when the dilation is not accompanied by a larger discharge. In other words, the heart is dilated during systole as well as diastole; a relation that may be expressed by the

volume curves diagrammatically shown in Figure 8, B. Let us hereafter refer to this type as pathological dilatation (myogenic dilatation of Moritz).

Pathologic dilatation is frequently attributed to a failure of cardiac tonus; the physiologic type, to a passive distention in which tonus persists. According to such conceptions, Patterson, Piper and Starling consider the term tonus "as synonymous with the physiological condition or fitness of the muscle fibers and its measure is the energy set free per unit length of muscle fiber at each contraction of the heart." A heart with good tonus will carry on a large circulation and nearly empty itself at each contraction, a heart with defective tonus can eject the same systolic volumes, only when its fibers are lengthened (Fig. 8, B). This is also essentially the conception formulated by Moritz.<sup>23</sup>

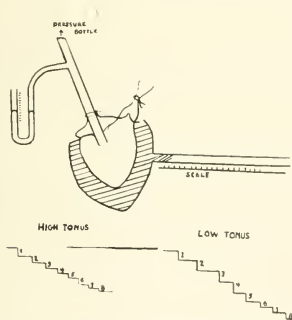


Fig. 9.—Diagram illustrating principle of measuring volume—elasticity coefficient of relaxed ventricles. Lower curves illustrate distention curves in heart with high and low tonus, each step representing an equal increment of intraventricular pressure.

While this expresses the end effects of tonus changes, and relates the importance of tonus to cardiac efficiency very well, it does not clearly define the nature of tonus itself, nor does it analyze the mechanisms through which tonus governs cardiac efficiency. To the physiologist, the term "tonus" has come to signify a sort of a sustained partial contraction of muscle tissue by virtue of which the muscle fibers resist stretching more than they would by virtue of the inherent elasticity

23. Moritz: Deutsch. Arch. f. klin. Med. 66:349, 1899.

alone. According to this conception, the ventricular tonus varies directly as the volume-elasticity coefficient of the relaxed heart, i. e., the ratio of the pressure increase to the volume increase,  $\frac{\Delta p}{\Delta v}$ .

This relation may be studied after the fashion schematically illustrated in Figure 9. Let us suppose that, in such a preparation, sufficient fluid is admitted into the ventricle to raise the intraventricular pressure by eight equal increments. The volume changes corresponding to each of, say eight, such pressure elevations may then be plotted in steplike fashion. Comparison of curves from ventricles under varying conditions of tonus make it quite obvious that when tonus is low, a much greater increase in volume accompanies a given pressure increase than when tonus is high; or, stated in the reverse, the same volume change is associated with a much greater pressure change when tonus is high than when it is low.

We may now again examine into the reasons why a heart with deficient tonus is less effective than the normal. Two hearts, distended to equal volumes, would have equal initial lengths. If this is the dominant or only factor determining the power of the heart to respond, we can only assign the decreased working capacity to an impairment of the muscular irritability itself. Such is apparently the conception of Starling and his associates. If, however, initial tension is primarily concerned in determining the working capacity of the heart, then the reduced working capacity of the ventricle during atonia may be accounted for by the fact that, at equivalent initial volumes, the initial pressure is lower in the atonic than in the normal heart.

The factors which may modify cardiac tonus have not all been definitely established on an experimental basis. Thus, from the experiments of Socin,<sup>17</sup> it could not be definitely ascertained whether in cardiac depression from chloroform, tonus was also reduced. Bruns,<sup>12</sup> however, was able to show definitely that tonus in the frog's ventricle is reduced when for long periods of time the heart is made to beat a very rapid rate, or compelled to work against increased resistance.

*Compensation and Decompensation.*—It is the dynamic function of the heart so to adjust its mechanisms that it, at all times, pumps the venous blood received into the systemic system under sufficient pressure to insure a continued capillary flow. As long as the heart does this, the circulation is compensated; when it fails to do so, decompensation occurs. The power of compensation is a physiological attribute of normal muscle tissues and is not necessarily linked with subsequent cardiac hypertrophy. This phase of the compensatory phenomenon may be well illustrated by reference to the acute production of a severe experimental lesion in animals. If, for example, the aortic valves are suddenly rendered incompetent, it will be found that the aortic diastolic-

pressure not only falls at once, but that the systolic pressure remains normal or rises above normal with the very next beat. The mechanisms through which this is accomplished operate somewhat as follows: With the first diastole, a small volume of blood regurgitates back into the ventricles. This not only distends the ventricles but elevates the initial tension. Consequently, during the next and every subsequent beat, not only the tension-maximum, but also the volumes ejected during systole are greater. Compensation for valvular defects then resolves itself into an increase in diastolic volume and initial tension which causes the heart to react, at once, by larger pressure curves and larger output.

Under what conditions does such immediate compensation fail to take place? Two suggest themselves: (1) If the tonus of the heart muscle, as defined, is low, augmented volumes may be accommodated within the ventricle without a proper elevation of initial tension. When this happens, the pressure-maximum reached within the ventricles and aorta are both lower and the discharge is actually decreased. (2) If the reserve power of the normal ventricle is exceeded, or, if, through depressing agents, the normal reserve power is reduced, then also, decompensation supervenes. This necessitates an interpretation in more precise physiologic terms of the phrase "reserve power."

We have seen that every increase in diastolic volume and initial tension causes not only a larger systolic discharge but a higher pressure-maximum within the ventricles as well (Fig. 7). To this, as it has been experimentally shown, there is, however, a limit, for, if the initial pressure increases more and more, there comes a time when the pressure-maximum begins to decrease. Then the systolic discharge also decreases. The initial pressure at which this turning point occurs may be taken as the index of the reserve power of the ventricles. Whenever, therefore, the increase in initial pressure occasioned by a valvular defect rises above this point, the efficiency of ventricular contraction diminishes and decompensation begins. This safety mechanism whereby the ventricle is capable of responding at any moment's notice to larger initial tension, undoubtedly explains why decompensation does not, as a rule, occur in valvular lesions for many years, and that patients remain quite unaware of valvular disturbances which may be very marked.

The initial pressure at which the heart no longer responds with more vigorous beats and normal systolic discharge varies, not only in different animals, but in the same heart, e. g., when its blood supply is altered or when the heart muscle has been submitted to toxic depression or long continued strain. We have in this a clear explanation as to just how the condition of the myocardium finally determines whether compensation or decompensation takes place. For years, experiments

on artificial circulation machines (Marey,<sup>4</sup> Moritz,<sup>24</sup> etc.) had demonstrated that, whenever left heart valvular lesions occur, there is always a physical tendency for blood to dam back toward the right side, thus increasing pulmonary and right ventricular pressures. On the basis of such physical experiments, clinicians have long explained the pulmonary congestion and venous stasis observed in cardiac cases on the so-called "back pressure theory." It was, therefore, surprising that practically all experimental investigations of the various heart lesions (MacCallum and McClure,<sup>25</sup> Straub,<sup>7</sup> etc.) show that "back pressure effects" occur very seldom in lesions acutely produced in normal hearts. How are these observations to be interpreted? The physics of the body circulation is not different from that of artificial circulation machines. Back pressure effects should be and, as a matter of fact, would be produced, were it not for the immediate compensatory reactions called into play. When, in animals or in patients, this compensatory mechanism (i. e., the ability to respond to increased initial tension and volume by equal discharge and higher pressure-maximum) is lost, decompensation sets in. Then, and then only, "back pressure effects" take place.

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24. Marey: *La Circulation du Sang* **16**:136, 710.

25. MacCallum and McClure: *Johns Hopkins Hosp. Bull.* **17**:260, 1906; **22**:197, 1911.

# INTERPOLATED CONTRACTIONS OF THE HEART WITH ESPECIAL REFERENCE TO THEIR EFFECT ON THE RADIAL PULSE \*

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## INTRODUCTION

Attention should be directed to some of the characteristics of interpolated contractions of the heart, particularly as they affect the radial pulse, since at times this type of cardiac irregularity is confusing.

An interpolated beat is a premature contraction of the ventricles which is not followed by a compensatory pause and does not disturb the dominant rhythm of the heart. It is impossible for auricular beats to be interpolated, because auricular premature beats are bound to disturb the dominant rhythm. It is also impossible to have interpolated beats in a case of complete auriculoventricular heart block, because here the dominant rhythm is ventricular, and so it, too, would be disturbed. Dresbach and Munford<sup>1</sup> state that interpolation in a case of Stokes-Adams' disease was reported by Lichtheim in 1905, but such a phenomenon is very unlikely. Inasmuch as interpolated beats can be no other than ventricular and must be premature, the cumbersome expression "interpolated premature ventricular contractions" can be discarded. In this paper we shall restrict ourselves to the term "interpolated beats." This form of premature beat is the only true "extrasystole," the term as it has been applied to the usual premature beat being unsatisfactory, since the heart rate in such a case is unchanged. Interpolated beats are relatively infrequent but not so rare as has been stated by some authors. The A-V conduction is usually delayed following the interpolated beat, causing a delay in the appearance of the next normal pulse wave (Figures 1, 2, 3 and 4).

The mistake most frequently made, in the instances where wrong interpretations of the arterial pulse occur, is in stating that two premature beats appear, one immediately following the other; the first beat, the interpolated one, being designated as the first premature beat, while the next, which is the normal, is called the second premature beat. Again, a confusing picture may be presented where the regular occurrence of interpolated contractions every third beat, failing to reach the

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\* From the Cardiographic Laboratory of the Massachusetts General Hospital.

I. Dresbach, M., and Munford, S. A.: Interpolated Extrasystoles in an Apparently Normal Human Heart, Illustrated by Electrocardiograms and Polygrams, *Heart* 5:197, 1913.

wrist, gives rise to pseudo-alternation. Three other very rare sources of error will be discussed later. This communication is presented in an effort to show wherein errors have been made and to simplify the diagnosis of this form of arrhythmia.

#### HISTORICAL

A résumé of the literature on this subject, up to 1914, appears in an article by Dresbach and Munford.<sup>1</sup> Busquet<sup>2</sup> stated that the first published tracing of interpolated beats was in the work of Marey,<sup>3</sup> in 1881. However, on examination no definite example was found by us among the 375 tracings in this book. It is possible that in Figure 355, page 723, such an irregularity appears, but it is more likely a bigeminal pulse due to very late premature beats. In an earlier publication by Marcy<sup>4</sup> a questionable interpolated beat appears in Figure 89, page 292. Uncertainty in diagnosis here is due to the fact that hiccup occurred at this moment, so that the picture is more likely the result of artefact. His Figure 202, page 524, may possibly contain interpolated beats.

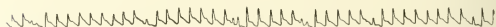


Fig. 1.—An arteriogram of T. O. showing clearly a typical curve of interpolated beats. Most of them can be easily seen; their amplitude varies and they are followed by normal beats of small size and delayed appearance. There is not always close relationship between the size of the interpolated beats and the size of the succeeding normal beats.

Wenckebach,<sup>5</sup> while correcting Mackenzie's error of interpreting an interpolated beat and its succeeding normal beat as two premature beats (Fig. 83, p. 99 of Mackenzie's "Study of the Pulse, Arterial, Venous, and Hepatic, and of the Movements of the Heart"<sup>6</sup>) fell into the same error in his interpretation of his own Figure 10. Here the great delay in the appearance of the normal beat undoubtedly misled him. He republished in his book on the arrhythm-

2. Busquet, H.: Les Extra-systoles sans Repos Compensateur, Arch. d. Mal du Cœur, Paris 5:187, 1912.

3. Marey, E. J.: Irregularités Périodiques du Pouls chez le Vieillard, Circulation du Sang, 1881.

4. Marey, E. J.: Physiologie médicale de la Circulation du Sang, Paris, 1863, Adrien Delahaye, Libraire-Editeur.

5. Wenckebach, K. F.: Zur Analyse des Unregelmässigen Pulses, Ztschr. f. klin. Med. 36:181, 1898.

6. Mackenzie, J.: The Study of the Pulse, Arterial, Venous, and Hepatic, and of the Movements of the Heart, 1902.

mias<sup>7</sup> this same tracing with the same interpretation. Figure 9 of his book is correctly interpreted. Mackenzie's<sup>6</sup> Figures 53 and 54 probably contain examples of this condition. Trendelenberg<sup>8</sup> published tracings demonstrating interpolated beats as they were produced experimentally in frogs' hearts. One year later, in Hoffman's<sup>9</sup> writings, a good example appears in a poor tracing (his Fig. 5). Here the picture of pseudo-alternation is produced by the occurrence of interpolated beats, every third beat failing to reach the wrist. The true condition was unrecognized by the author. Also in 1904 Volhard,<sup>10</sup> in a paper on "Ventricular Bigeminy without Compensatory Pause, Resulting

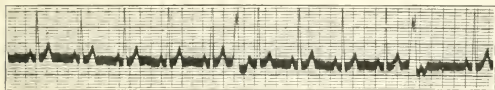


Fig. 2.—Electrocardiogram of T. O., Lead II. Here are shown premature beats of two types: the first interpolated; and the second a premature ventricular contraction with compensatory pause. The stimuli which provoke each contraction arise from the same point of the right ventricle in each instance. The *P-R* interval after the premature beat is greater than the *P-R* interval which precedes it.

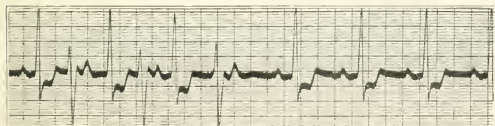


Fig. 3.—Electrocardiogram of Y (Lead II), a case of prolonged A-V conduction. The second and fourth contractions of the series are interpolated. The A-V conduction time is lengthened after the first, but practically no lengthening occurs after the second. The sixth beat is a premature contraction of the ventricle with full pause following. The remaining part of the curve is of normal rhythm, the prolonged conduction time being evident. All the premature beats arise from the same focus of left ventricle whether they are interpolated or not. The T wave shows evidence of digitalization.

7. Wenckebach, K. F.: *Die Arrhythmie als Ausdruck Bestimmter Functionsstörungen*, Leipzig, Verlag von Wilhelm Englemann, 1903.

8. Trendelenberg, W.: Ueber ein Wegfall der Compensatorische Ruhe am Spontan Schlagenden Froschherzen, *Arch. f. Anat. u. Physiol., Physiol. Abt.*, 1903.

9. Hoffman, A.: Ueber Verdoppelung der Herzfrequenz nebst Bemerkungen zur Analyse des Unregelmässigen Pulses, *Ztschr. f. klin. Med.* **53**: 1904.

10. Volhard, F.: Ueber Ventriculare Bigeminie ohne Compensatorische Pause Durch Rückläufigen Herzkontraktionen, *Ztschr. f. klin. Med.* **53**: 475, 1904.



from Retrograde Ventriculo-Auricular Contraction," in his Figure 8 interprets the tracing as an interpolated contraction. By accurate measurements of the radial curve in this figure it is obvious that a pairing of premature beats occurs, no interpolation taking place. Pan<sup>11</sup> shows two striking demonstrations of the irregularity. In his Figure 15, a tracing from the cubital artery, interpolation occurs, the beat failing to appear in the sphygmographic curve. The succeeding normal beat is delayed and decreased in amplitude. There is also shown very clearly in Figure 23 the failure of an interpolated beat to reach the wrist, with marked delay and decrease in size of the next normal wave. Hay's little volume<sup>12</sup> contains three curves with all the interpolated beats coming through, the next normal beats being only slightly smaller

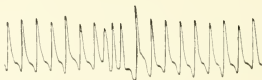


Fig. 4.—A radial curve of A illustrating what at first glance might be called a short paroxysm of tachycardia. On closer inspection it proves not to be. The first beat of the run of four is normal, the second interpolated, the third normal (slightly retarded) and the fourth a ventricular premature contraction with compensatory pause.

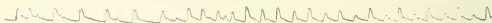


Fig. 5.—Radial tracing of E. D. showing an arrhythmia due to numerous interpolated contractions, in the last half of the tracing occurring every third beat and giving rise to a well-marked pseudo-alternation. There is delay in the small beats with non-appearance of the interpolated beats. In the middle of the tracing two of the interpolated contractions are clearly seen. At the beginning of the tracing there is an ordinary bigeminal pulse due to ventricular premature contractions every second beat, followed by compensatory pauses.

than the preceding normal pulse waves. Prolongation of the As-Vs interval following the interpolated beat is discussed by this author. Laslett,<sup>13</sup> in discussing a case showing the "Regular Occurrence of

11. Pan, O.: Ueber das Verhalten des Venen Pulses bei den durch Extrasystolen verursachten Unregelmässigkeiten des menschlichen Herzens, *Ztschr. f. Exp. Path. u. Therap.* 1:57, 1905.

12. Hay, J.: *Graphic Methods in Heart Disease*, 1907.

13. Laslett, E. E.: The Regular Occurrence of Interpolated Extrasystoles, *Heart* 1:83, 1909-10.

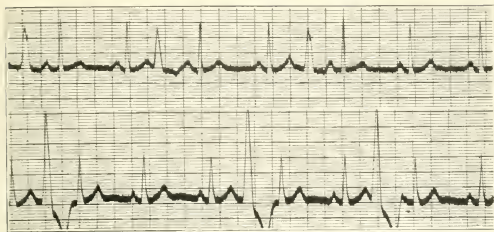


Fig. 6.—An electrocardiogram, Leads I and III, of E. D. Three interpolated contractions appear in Lead I and following each the *P-R* interval is slightly lengthened. Three interpolations are seen also in Lead III. This electrocardiogram confirms the interpretation of the radial tracing of Figure 5. Abscissa = 0.2 sec., ordinate = 10.4 volt. These same measurements apply to the electrocardiograms following.

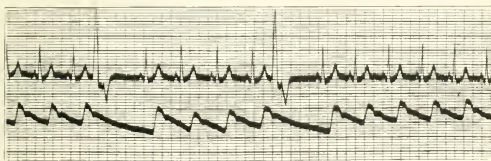


Fig. 7.—Simultaneous electrocardiogram (Lead II) and sphygmogram from radial artery (E. D.). This and the three following figures are from the same patient, all taken on the same occasion. Here is seen the appearance of premature ventricular contractions at two points; in neither instance does the heat show in the radial curve.

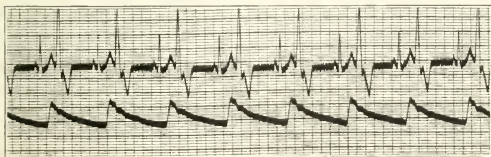


Fig. 8.—Simultaneous electrocardiogram (Lead II) and arteriogram (radial) (E. D.) which shows a perfectly regular radial pulse with a rate between 40 and 50 per min., the result of the regular occurrence of premature ventricular contractions every second beat, failing to reach the wrist.

Interpolated Extra-Systoles," states that the marked prolongation of the As-Vs interval following the interpolated beat does not seem to be the rule, the exact significance of this factor with regard to the origin of the compensatory pause not being clear. An excellent illustration of pseudo-alternation due to interpolated beats every third beat, not reaching the radial curve, is given by Gallavardin and Gravier.<sup>14</sup> The small normal contractions are considerably delayed. An incorrect interpretation by Mackenzie in his "Diseases of the Heart"<sup>15</sup> (p. 208, Fig. 118), is indicated by analysis of the jugular pulse tracing. Undoubtedly, the delay in the appearance of the normal beat, marked by Mackenzie as

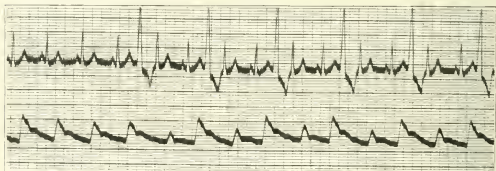


Fig. 9.—Simultaneous electrocardiogram (Lead II) and radial curve (E. D.).<sup>\*</sup> A short phase of normal rhythm is interrupted by an interpolated contraction, which irregularity persists throughout the remainder of the tracing. The occurrence of the interpolated beats every third beat and their failure to come through to the radial artery gives a characteristic picture in the sphygmogram.

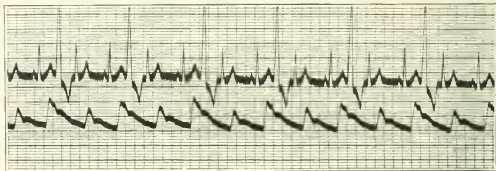


Fig. 10.—Simultaneous electrocardiogram (Lead II) and radial tracing (E. D.). Interpolated contractions occur regularly every third beat producing very prettily a picture of constant alternation in the sphygmogram. With the electrocardiographic curve as a guide in this case, the interpretation of the arteriogram is very simple.

14. Gallavardin, L., and Gravier, L.: Quelques Particularités de l'Alternance du Poulx: Variété du Poulx Pseudoalternant; Couples Extra-systoliques et Alternances; Changements de Sens Spontanés de l'Alternance, Arch. d. mal. du Cœur 7:497, 1914.

15. Mackenzie, J.: Diseases of the Heart. Ed. 3, 1913.

the second  $r'$ , misled him. The high wave in the jugular pulse during the long radial intermission is made up of  $a$  and  $c$  and not  $a$  alone or  $a$  and  $v$ . There occurred here an alternation of the normal and premature beats, the first premature beat interpolated and the second following by a compensatory pause but failing to reach the wrist. In "Clinical Cardiology"<sup>16</sup> Neuhof published a radial tracing (Fig. 153, p. 71) the small beat of which he refers to as "an extrasystole which is not premature"; the disorder is almost certainly due, however, to the interpolation of a contraction which failed to reach the wrist, but which reduced in size and delayed the next normal beat. Lewis<sup>17</sup> gives a few curves showing interpolation. Figure 165, page 208, in his new edition, is an electrocardiogram in which there are two interpolated contractions, with very slight As-Vs lengthening following them. Also, Figure 164, page 208, a simultaneous record of electrocardiogram, phlebogram and sphygmogram, contains a single interpolated beat. This fails to change the sphygmogram, except to delay the next normal wave about one-tenth second. Length-

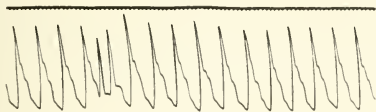


Fig. 11.—A sphygmogram of S. showing four beats of the normal rhythm followed by an interpolated contraction. The succeeding beat, the normal, is slightly delayed and decreased in amplitude. Time intervals 0.2 sec. In all further arteriograms the same time interval is recorded.

ening of the P-R interval occurs. Lewis states that the reason for the prolongation is obscure since the extra beat has not been propagated through the A-V bundle. However, it may have traversed the A-V bundle and been stopped at the auriculo-nodal junction which is the point of greatest retardation in the A-V conduction. Lewis' statement that the larger the pulse wave of the interpolated beat, the smaller is the succeeding pulse, is not always borne out (see our own Figure 1). Figure 98, page 150, of Lewis' new edition,<sup>17</sup> an experimental curve from the dog's carotid simulates very closely the picture produced in man by an interpolated beat failing to reach the wrist followed by a weak normal wave. A simultaneous curve taken directly from the ventricle proves that the weak beats are much delayed premature ven-

16. Neuhof, S.: Clinical Cardiology, 1917.

17. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, 1920.

tricular contractions, and not due to normal beats delayed as the result of interpolated contractions which failed to reach the carotid. This possibility must be kept in mind in the arterial tracings from man, although, as Lewis states, "it is but rarely responsible for an inaccurate interpretation."

#### OCCURRENCE

Among 5,000 electrocardiographic plates taken of 2,392 subjects in the Cardiographic Laboratory of the Massachusetts General Hospital from 1914 to 1920, ventricular premature beats occurred in 284 plates of 200 patients, not including the ectopic beats of auricular fibrillation or of complete heart block. They were interpolated in twenty-four of these plates (8 per cent.), and in fourteen patients (0.6 per cent. of total patients, and 7 per cent. of cases showing premature beats). After for-

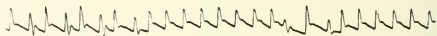


Fig. 12.—Radial curve beginning as bigeminy due to interpolated contractions every third beat, failing to reach the wrist. Then follows a phase of normal rhythm, a premature ventricular contraction with compensatory pause, and an interpolated beat, which does not come through.

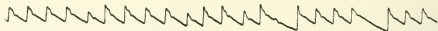


Fig. 13.—A sphygmogram in which an interpolated contraction occurs immediately after the fourth beat of the normal series and fails to show in the curve. A delayed small normal beat follows; then a run of four normal waves and the process is repeated. Two more normal beats come through and we see the same anomaly again. The last two interruptions are the result of premature contractions of the ventricle with compensatory pauses.

ty-two interpolated beats of these fourteen patients, there was definite prolongation of the P-R interval; in three instances there was no prolongation; and in thirty-four the prolongation was questionable. In one case it was observed that in the presence of sinus arrhythmia associated with interpolated beats, during the rapid rates of the auricular pacemaker, the P-R interval was much delayed, but that it was normal or only slightly delayed during the slower intervals.

The significance of the interpolated beat is just that of the premature ventricular beat generally—that is, the interpolated beat is evidence of an irritated heart, but not necessarily of heart disease. Its

presence adds nothing to the prognosis of a given case. Of our fourteen patients, six showed evidence of heart disease; four were questionable, and the other four showed merely an irritated heart. One of the last four, (Figs. 5, 6, 7, 8, 9 and 10) has had an intermittent pulse for fifteen years, but has had no other cardiac symptoms than the occasional palpitation. The interpolated beat is merely a rare variety of premature ventricular contraction. Nearly every case showing it also shows at other times the usual ventricular premature beat with compensatory pause. The slower the pulse the more apt is the ventricular premature contraction to be interpolated, for in such an instance the ventricle will have recovered from its refractory phase following its interpolated contraction when the next normal auricular impulse reaches it.

#### DIFFERENTIAL DIAGNOSIS

The interpolated beat in the arteriogram must be differentiated especially from two other conditions with which it is apt to be confused. These are: (1) the occurrence of successive ventricular premature contractions; and (2) *pulsus alternans*. In the historical résumé we have already mentioned this possibility of confusion. Without venous pulse tracings or electrocardiograms the diagnosis may at times be difficult.

Often the analysis of the radial tracings where interpolation occurs is simple, the interpolated beat fitting in between two normal beats with very little delay in the time or decrease in the amplitude of the second normal beat (Fig. 11). The occurrence of two successive ventricular beats is uncommon. In the Cardiographic Laboratory of the Massachusetts General Hospital, among 260 electrocardiograms of 186 patients showing premature ventricular contractions (not including those showing interpolated beats together with premature ventricular contractions with pauses) pairing of these premature beats was found in twenty-one plates. There was a total of ninety-eight instances of pairing, seventy-four of these having occurred in nine plates of one patient. Therefore, leaving out of consideration this one case in which they occurred so frequently, we have the appearance of consecutive premature contractions twenty-four times in only twelve out of the 251 different plates of 185 patients. Among these ninety-eight instances where pairing occurred, accurate measurement was possible in only sixty-five, and in only six of these did the interval during the pairing equal the space between two normal beats. In three instances the interval was equal to the space between three normal beats, which condition cannot occur in the case of interpolated beats. In the other fifty-six instances the space over the pair was unequal to either two or three normal beats but fell between these two measurements or between

the measurements of three and four normal beats.<sup>18</sup> When in doubt, an electrocardiogram is necessary to distinguish between the interpolated beat disorder and the occurrence of a pair of ventricular premature beats.

The second condition which may be confused with interpolated contractions is constant alternation of the pulse, in which the weak beats are considerably delayed (Figs. 5, 10 and 12). This difficulty occurs rarely, because it necessitates the absence in the radial pulse of all evidence of the interpolated beats themselves. In such a case an electrocardiogram or jugular pulse tracing clears up the situation at once. We have found constant alternation much more common than constant pseudo-alternation due to interpolated beats. In only two cases have we discovered this type of pseudo-alternation, a possibility rarely recognized.

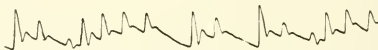


Fig. 14.—Tracing from radial artery. Near each end of the curve two very small waves are seen. These are the normal contractions which have been preceded by interpolated beats failing to show in the tracing. Near the center the two long intermissions are produced by ventricular premature contractions, failing to reach the artery, and followed by full pauses.

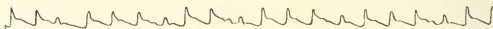


Fig. 15.—A sphygmogram of T. O. illustrating a premature ventricular beat of the usual type, it being at the first point of interruption of the regular rhythm in the tracing. Then follow three normal beats. In the remainder of the curve four interpolated beats varying in amplitude occur, and in each instance a small delayed normal contraction follows.

A third possible source of error in the analysis of radial tracings in arrhythmia due to interpolation is the infrequent return to one-to-one rhythm for three beats in long stretches of two-to-one auriculoventricular heart block. In both instances the time of the two short intervals is greater than that of one long space because of the increase in the P-R interval. In such rare instances electrocardiograms or jugular pulse tracings are necessary for differentiation. We have seen one

18. This break in the dominant rhythm is due to retrograde contraction of the auricle following one or the other or both of the ventricular premature beats.

such case of heart block which might be confused with the interpolated contraction, but the radial pulse was not of characteristic form.

A fourth arrhythmia to be differentiated from the interpolated beat in the arteriogram is the premature ventricular contraction occurring at every fourth beat and failing to reach the wrist. Here, also, venous pulse tracings or electrocardiograms quickly differentiate, but the arteriogram itself is usually quite different in form from that of the interpolated beat arrhythmia in that the beats of the normal rhythm are evenly spaced and uniform in amplitude, which is not the case in interpolation.

A fifth condition to be considered in the differential diagnosis are short runs of paroxysmal tachycardia. Occasionally, one finds interpolated beats occurring every other beat, as in Dresbach and Munford's<sup>1</sup> case, and for a few beats in our Figure 3. In this figure two such interpolated beats are shown, and the third beat is followed by a compensatory pause. The pulse, upon palpation or auscultation of the heart, would have shown in this case six beats in rapid succession and might have simulated a short paroxysm of tachycardia. In

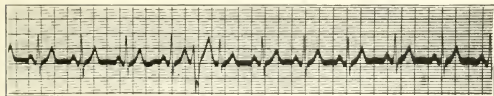


Fig. 16.—An electrocardiogram of S. T. in which one interpolated contraction occurs after the fourth beat of the normal rhythm. The large wave succeeding results from the falling together of the *T* and *P* waves. Note the lengthening of the *P-R* interval after this contraction.

Figure 4 there is shown a short phase of four beats in rapid succession. Here the interpretation undoubtedly is as follows: the first of the four is normal, the second is an interpolated contraction, the third is normal, and the fourth a premature ventricular contraction followed by a compensatory pause.

Figures 13 and 14 illustrate two radial pulses difficult at first glance to interpret. In Figure 13 two long pauses appear in the tracing, one with a poorly marked premature beat in evidence, while in the other a premature beat takes place but is not forcible enough to come through and appear in the curve. At the beginning and middle of the tracing are three delayed and diminished beats which follow interpolated contractions too weak to reach the radial artery. It is this abnormality in the arteriogram which has puzzled a good many students but which is perfectly typical and easily recognized as soon as one is familiar with it. Figure 14 shows likewise two small beats which are the normal



contractions following interpolated beats, not reaching the wrist. Two long intermissions are also seen due to premature ventricular beats with compensatory pauses. These also do not appear.

Figures 7, 8, 9, and 10 are tracings from a single patient who has shown various forms of arrhythmia of the pulse as a result of premature ventricular and interpolated beats. In Figure 7 are shown simple premature beats with pauses, the beats not coming through to the wrist. Figure 8 shows the regular occurrence of premature contractions every second beat, none of them being forcible enough to produce a wave. It illustrates a slow, dead regular pulse the palpation of which, alone, at this particular time would not suggest the presence of premature beats. In Figure 9 we note the onset of a phase of arrhythmia due to interpolated beats, every third beat not coming through. And Figure 10 shows a continuation of this same rhythm. These last two illustrations show in a very clear manner the mechanism of the usual effect on the radial pulse of interpolated beats and illustrate one type of pseudo-alternation. If the reader will familiarize himself with the arrhythmia found in these figures he will save a good deal of effort in the future in analyzing such curves.

#### SUMMARY

There is here given a brief historical review of the subject of interpolated beats. Figures are given stating the frequency with which interpolated beats and premature ventricular contractions have been found in the graphic records of the Cardiographic Laboratory of the Massachusetts General Hospital. Points in regard to the differential diagnosis of this form of arrhythmia are discussed; the five conditions from which it must be differentiated in the arterial pulse being: first, the occurrence of two premature ventricular beats in succession; second, constant alternation of the pulse in which there is a delay in the weaker beats; third, auriculoventricular heart block associated with an occasional return to one-to-one rhythm for three beats in long stretches of two-to-one rhythm; fourth, arrhythmia due to the premature beats every fourth beat which fail to appear in the arteriogram; and fifth, short paroxysms of tachycardia. Emphasis is laid upon that type of tracing which is most frequently misinterpreted, namely, where in the course of a phase of regular rhythm there occurs an interpolated beat which, not showing in the curve, causes a delay and diminution in the size of the next normal wave. Insufficient emphasis has been put in the past on this abnormality in the arteriogram, and it is on this that we lay special stress.

## BOOK REVIEW

PRINCIPLES OF HUMAN PHYSIOLOGY. By ERNEST H. STARLING, C.M.G., F.R.S., etc., Jodrell Professor of Physiology in University College, London. The chapter on the sense organs revised and largely rewritten by H. Hartridge, M.A., M.B., Cantab. Ed. 3, with 579 illustrations, 10 in color. Philadelphia, Lea & Febiger, 1920.

The success of Starling's Physiology, as shown by reaching a third edition in eight years, is to be explained by the author's high standing as experimenter and teacher, by the clearness of the statement and well chosen arrangement of the work, and these warrant its use by beginners. There is one curious feature, over 100 pages, or almost one-eleventh of the total space, is devoted to vision. Perhaps, the vagaries of the medical book trade are to blame for this; perhaps, lack of time to condense the material into space proportionate to that of other topics. In strong contrast to this large chapter, the ear and its associated organs are discussed in a few pages. Perhaps, Bárány's work was made too prominent by certain specialists during the war, but that seems all the greater reason why a clear and authoritative summary should be given.

Readers of the ARCHIVES OF INTERNAL MEDICINE are not much interested in a work on physiology prepared for beginners. When a large volume appears, they turn to it for definite reasons. They may wish to review again the whole subject. If so, they will find much of interest in the chapters on the Structural Basis of the Body and on the Material Basis. They will be interested in seeing that the word "proteid," preferred by some writers, is avoided by the author on account of its misleading use. They will find much clarifying discussion on colloids, ferments, electric changes in muscles and nerves. Those who seek information on topics much written about in current journals, but little known in undergraduate days, will often be disappointed. The chapter on metabolism is clear, concise and accurate as far as it goes, but of little assistance to the physician who wishes to get his knowledge abreast of the times by taking a laboratory course. One who is puzzled by statements about respiratory quotients, for example, will have trouble coordinating the information scattered over several different sections. Everywhere the lack of reference will disappoint the mature reader, or in fact, anyone qualified to read a textbook of 1300 pages. The brief remarks on vitamins is characteristic of many parts that read like abstracts noted for further elaboration. The practitioner or the young researcher who seeks an up to date presentation of the subject of digestion will find a praiseworthy impartiality as to the identity of rennin and pepsin. He will find mention of Pawlow, even a reference to the English translations of the work on the digestive glands, also to Cannon, but of other, more recent writers, not a word. Clinical references are conspicuous by their absence. It is all the more striking to find under "gout" the statement that "in normal individuals the amount of uric acid in the blood is too small to be detected." The reader seeking recent light on the D:N ratio will look in vain in the index, but will find the subject well stated in the chapter on the history of fat in the body. Alkaline reserve and hydrogen ion concentration are adequately presented. Can the young clinical pathologist get any satisfaction from the statement that blood platelets are "precipitates produced in the plasma directly it undergoes alterations"? Should not the fact that there is an auscultatory method in blood pressure determination be, at least, indicated? The older practitioner, puzzled by the flood of electrocardiographic papers, and turning to Starling for the explanation of auricular fibrillation, will find nothing in the index and little in the text. That little is good, though dogmatic and undocumented. Extrasystole does not fare so well. If the author knows the record of pulse rates of 30 and 120 in men otherwise

perfectly healthy, references would seem worth while. Very satisfactory are the chapters of cellular and chemical methods of defense, also that on the chemistry of the respiration, as was to be expected. The author is rarely finicky, but what else can one call it when he criticizes the common use of "expiratory dyspnea." Perhaps, it is a slip of the pen that translates 37 C. as 98.4 F. instead of 98.6 F. The chapters on urine are good, Cushny's work being mentioned often. That on the ductless glands is too short. On the whole, Starling is not likely to be used much after undergraduate days. Perhaps, the belief that it will not be used explains the poor paper and the flimsy binding, or is the latter an indication of sabotage? The reviewer's copy has the text fastened to the back only by what looks like mosquito netting.

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# Archives of Internal Medicine

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No. 5

## STUDIES ON THE RESPONSES OF THE CIRCULATION TO LOW OXYGEN TENSION

### III. CHANGES IN THE PACEMAKER AND IN CONDUCTION DURING EXTREME OXYGEN WANT AS SHOWN IN THE HUMAN ELECTROCARDIOGRAM \*

CHARLES W. GREENE, PH.D., AND N. C. GILBERT, M.D.  
COLUMBIA, MO. CHICAGO

Anoxemia in the normal man can safely be carried to the stage of unconsciousness when produced by the process of continuous and gradual reduction of the oxygen in the air breathed. The responses of the body to the gradual oxygen reduction are compensatory to a certain limit. The crisis appears promptly when the compensating limit is reached for any particular person and set of experimental conditions until in rapid succession the following states are passed: (1) Decrease and loss of attention; (2) loss of voluntary control of muscles, and (3) complete unconsciousness but with a degree of reflex control of voluntary muscles. The heart beat and respiratory movements persist through these three cycles. The degree of circulatory efficiency at the onset of unconsciousness is adequate for the moment, but is assumed, in general, to be failing rapidly.

We have applied the methods of the electrocardiograph to the study of the changing function of the human heart through all stages of the symptoms of low oxygen from the normal to unconsciousness and collapse. Twenty-one cases are recorded in this paper.

The physiology of the human at high altitude has received consideration for the last half century, and the literature is now rather definite and in harmony as to the main causal explanations. The reader is referred to the phenomena described as mountain sickness by mountain climbers, or altitude sickness of balloon men, and to the corresponding symptoms detailed by those who have investigated the problem of low pressure chambers and of airplanes. The work of Paul Bert,<sup>1</sup> published in a series of scientific papers at intervals from 1871 to 1874 and in book form<sup>2</sup> in 1874 (summary) and 1878, of

\* The experimental data detailed in this paper were obtained in a special study carried on under the orders of the Surgeon-General's Office, Division of Aeronautics.

1. Bert: A series of thirteen articles published from 1871 to 1874. *Compt. rend. Acad. d. sc.* **73**:213, 503, 1871; **74**:617, 1872; **75**:29, 88, 491, 543, 1872; **76**:443, 578, 1276, 1493, 1873; **77**:531, 1874; **78**:911, 1874.

2. Bert: *La Pression Barometrique*, etc., Paris, 1874 and 1878.

Mosso,<sup>3</sup> of Zuntz,<sup>4</sup> and the more exhaustive Pike's Peak studies of Douglas, Haldane, Henderson and Schneider,<sup>5</sup> have given the facts in the physiologic responses of the body in great detail. This accumulated altitude physiology became of immediate practical value with the development of the aviation program of the United States, and served as the scientific basis for the establishment of the Medical Research Laboratory of the Air Service.

Instances of unconsciousness developed in the air are related by men in the Air Service. Many aviation fatalities are thought to be due to this cause. Instances of unconsciousness or partial unconsciousness with physical distress developed at high altitudes have ended in recovery on descent to lower atmospheric levels. The experimental observations of the Medical Research Laboratory recorded in the Air Service Medical<sup>6</sup> support the view that these problems of altitude are not so much the effects of decrease in barometric pressure, or of temperature changes, but are primarily due to oxygen want.

The cardiac accelerations of rate due to progressive oxygen want were first described by Bert<sup>7</sup> in the experimental production of low atmospheric pressure in the low pressure chamber. Bert showed also that the accelerations were removed on giving oxygen in the chamber. The changes in rate are given in fuller detail with numerous illustrations, both for the low pressure chamber and the rebreather, by Schneider,<sup>8</sup> Whitney<sup>9</sup> and more fully in the Air Service Medical. Coincident changes in blood pressure, respiratory volume and alveolar air have been compared by Lutz and Schneider<sup>10</sup> and by Gregg, Lutz and Schneider.<sup>11</sup> The summarized facts and interpretative views may be stated categorically for the heart as follows: The heart rate augments during oxygen reduction. Acceleration is slight and very gradual in the early stage of reduction, becomes more pronounced at from 15 to 12 per cent. oxygen, and very profound at the lowest limit of endurance by the individual, which may reach 7 or even 6 per cent., from 53 to 45 mm. partial pressure, in men of the highest oxygen resistance. Heart strain with dilation, circulatory collapse and fainting are described and emphasized by Whitney as a terminal condition to be avoided.

3. Mosso: *Life of Man on the High Alps*, London, 1898.

4. Zuntz, Loewy, Müller and Caspari: *Hohenklina und Bergewanderung*, etc., Berlin, 1906.

5. Douglas, Haldane, Henderson and Schneider: *Phil. Tr. Roy. Soc.*, London, Series B, **203**:271, 1913.

6. *Air Service Medical*: U. S. War Department, Government Printing Office, 1919.

7. Bert: *Compt. rend. Acad. d. sc.* **78**:911, 1874.

8. Schneider: *J. A. M. A.* **71**:1384 (Oct. 26) 1918.

9. Whitney: *J. A. M. A.* **71**:1389 (Oct. 26) 1918.

10. Lutz and Schneider: *Am. J. Physiol.* **50**:228, 280, 327, 1919.

11. Gregg, Lutz and Schneider: *Am. J. Physiol.* **50**:302, 1920.

Of the points summarized, the variations in heart rate may be accepted without question. The seven thousand and more records of official tests of aviators substantiate these facts. On the other hand, the cardiac dilation assumed on the basis of percussion has been more and more strongly questioned as the tests have accumulated. The determination of relative cardiac volume, minute by minute, is, in fact, fraught with great difficulty. The usual palpation and percussion methods are scarcely accurate enough to decide the point. The roentgen-ray method yields results that must be correlated with the phases of both the cardiac cycle and the respiratory movement, which for the moment vary the size of the heart. Majors Le Wald and Turrell<sup>12</sup> have applied ingenious devices to secure photographs at corresponding phases of the heart and respiratory cycles in their roentgen-ray studies of the size of the heart during progressive low oxygen induced by the rebreather method. They find little evidence of change of heart volume. This finding accords with the measurements of the circulation volume by Schneider and Sisco on Pike's Peak,<sup>13</sup> data from which the conclusion was drawn that the heart volume does not change with the increase of rate up to the altitude of Pike's Peak, i.e., 14,110 feet. However, 14,000 feet does not reach the straining limits of compensation for the average vigorous man. From 20,000 to 30,000 feet, and more, must be reached to produce the extreme vascular changes. Le Wald and Turrell describe one case of unconsciousness at the moment of a roentgen-ray exposure. This heart was not dilated. On the contrary, its outlines and volume were notably less than those shown by pictures taken at earlier stages of oxygen want from the same officer.

#### THE ELECTROCARDIOGRAPHIC METHODS

Electrocardiograms offer an added approach to the state of the heart under oxygen want. The method cannot lay claim to even a probable solution to the heart volume problem. But it ought to yield facts of value to the interpretation of the physiological state of the heart under extreme low oxygen stress and the possible source of the collapse in the circulatory system.

The electrocardiographic method is the present reliance for the determination of the following points in heart physiology:

1. The place of origin of the automatic excitation process.
2. The state, rate and direction of conduction of the excitation over the heart.
3. The degree of coordination of different parts of the heart.
4. The character of extra systoles of diverse types.

12. LeWald and Turrell: *Am. J. Roentgenol.* **7**:67, 1920.

13. Schneider and Sisco: *Am. J. Physiol.* **34**:1, 1914.

The oxygen want test was given to twenty-one individuals from whom electrocardiograms were taken at stated intervals during the tests. The experiments were made at the U. S. General Hospital No. 9, at Lakewood, N. J., March 5 to 12, 1919. All the necessary rebreather apparatus and the staff of assistants were taken to the Lakewood Hospital from Hazelhurst Field, Long Island. This secured to us the facilities of the excellent electrocardiographic station at Hospital No. 9.

The procedure was, in brief, to give the official rebreather test on the Larsen-Pierce type of rebreather. During the test the systolic and diastolic blood pressures, the heart rates, the respiratory movements, the respiratory minute-volumes, and the clinical state of the individual were all taken as described in the statement of methods in the various papers from the Medical Research Laboratory.

Electrocardiograms were taken for periods of about twenty seconds each, at five minute intervals, until the critical period or final failure of compensation approached. In most tests the interval was reduced to two minutes after the twentieth minute. At the critical moment and on signal from the clinician, a continuous electrocardiogram was taken until the end of the test. A final tracing was then taken after one or two minutes, and while recovery was in progress. Occasionally, due to the rapid onset of symptoms of oxygen want, the terminal tracing was missed, or the last asphyxial tracing was extended across to the recovery period. Through the hearty cooperation of the enlisted personnel of the Lakewood Hospital, splendid rebreather tests were carried to the limits of consciousness, and in several instances even beyond the point of complete loss of motor control by the central nervous system.

Loss of continuous attention and of voluntary motor coordination are the usual signs for terminating an official rebreather test. But heart and circulatory compensations continue several seconds longer, i. e., certainly until complete unconsciousness occurs. This is the rule. In exceptional cases, circulatory failures of compensation rather than failure of nervous coordinations occur at relatively high percentages of oxygen.

The official psychologic and ocular tests in use at the central laboratory at this time were abandoned as unnecessarily complicating this research. In judging the safe terminal limits of endurance, reliance was placed on the recorded evidences of compensations of respiratory volume, the coincident heart rate and blood pressure, and the general clinical signs of distress. The men who take this test, even to the limit of unconsciousness, recover very promptly after one or two inhalations of ordinary air. The delay is only a question of a few seconds, and the subject tested cannot believe that he has not been continuously

conscious. Friendly and keen rivalry among the men at Lakewood often led to protest that they had not yet reached their altitude limits, which indicates the absence of physical stress.

#### GENERAL EXPERIMENTAL RESULTS

Our results are presented in two groups. First, and briefly, the general observations necessary to the interpretation of the electrocardiographic results; second, the details of the changes in the heart recorded by the electrocardiograph. The general changes have to be kept clearly in the foreground that one may correctly interpret the changes in the heart itself.

By our method we not only record the electrocardiograms but also the respiratory rate, amplitude and volume. We take clinical observations of the heart rate and measure the blood pressures every minute by the sphygmomanometer method. The clinical aspect of the changes we present by a series of protocols and graphic charts (Figs. 1 to 7). Numerous published typical charts of this test are available in the Air Service Medical.<sup>6</sup> Only the cases of special interest in our series are charted here.

The chart presented for H. B. D. (Fig 1) serves very well to emphasize the critical points in the interpretation of the clinical results. His heart rate gradually increased from a minimum of 82 per minute to a maximum of 114 in the twenty-sixth minute when the break occurred. The systolic blood pressure increased during the run from 128 mm. to 152 mm. at the break. The diastolic pressure ran evenly enough at 70 mm. to the nineteenth minute, then progressively and rapidly fell to 50 at the break, 34 at the last reading. Up to the point of breaking, this record is a fairly typical one in regard to the compensatory responses of the circulatory system. Although the systolic pressure was always somewhat high for an average individual, the respiratory minute volume remained very low and irregular to the twenty-third minute, when it rapidly increased from 70 to 104 deciliters per minute. This was a strong test to 6.7 per cent. oxygen, over 29,000 feet equivalent elevation and over 27,000 feet when systolic pressure began to fall. The weakest clinical factor is apparently in the respiratory apparatus which did not compensate enough to prevent collapse, unconsciousness, clonic spasms and circulatory failure.

Comparing the seven charts it is obvious that F. J. D. (Fig. 2) also failed because of the respiratory deficit. J. F. (Fig. 3) collapsed at 8.4 per cent. oxygen from general failure of compensation in both blood vascular and respiratory mechanisms. His systolic pressure decreased from the beginning. There was some cardiac acceleration but absolutely no respiratory response. The limit of the endurance of T. H. K. (Fig. 4) was over 28,000 feet, 7.1 per cent. oxygen. In his case



there was inadequate circulatory compensation. The lowest oxygen endured in this series was W. C. M. (Fig. 5) at 5.9 per cent. altitude, over 31,000 feet. This was accomplished largely by virtue of an extraordinary response of the respiratory apparatus and a rising blood pressure. Even at that altitude (Plate 4) only the slightest shift in the locus of the point of origin of the heart beat occurred. The collapse of T. B. M., like that of J. F., was a failure of compensation in blood pressure. Both systolic and diastolic pressure fell from the start. The increase in heart rate and change in respiratory volume is not adequate as the final break showed. The profound heart failure in D. W. O. (Fig. 7) came at the comparatively high oxygen level of 8.5 per cent. This case is a fine example of a noncompensating type which endures oxygen want to its particular limit, then suddenly and without warning collapses.

The cases are fully illustrated because they fall in the class that gave cardiac breaks, and are all good tests for rather extreme low oxygen endurance. In fact, 8.5 per cent. oxygen is the highest of the lot. And while the cause of failure is more or less easy to interpret, it is also true that the tests were deliberately pressed to the extreme to secure data on the postcrisis and collapse stage. The cases are, therefore, not to be regarded as being pathologic.

The tests on seven out of twenty-one men examined gave valuable postcrisis data in cardiac behavior, and this data will be presented in full detail in the protocols.

#### ELECTROCARDIOGRAPHIC RESULTS

The electrocardiographic data are presented in detail in tables of measurements of cardiograms taken at intervals during the tests and the tables are supported by photographs of selected pieces of electrocardiograms. The protocols, tables, and plates give the first published data on the terminal stress of progressive oxygen want on the human heart, an adequate justification for full presentation of the data. Nevertheless, we have many additional cases and much evidence in reserve supporting the cases presented.

Profound changes are revealed in the physiology of the heart in the seven extreme tests featured. But take it all in all, the entire series shows a wonderful amount of endurance to oxygen want on the part of the human heart. Rarely does any serious interference with the normal cardiac behavior occur up to the stage which marks the borderland between loss of individual efficiency and complete unconsciousness.

The R-R interval is, of course, a function of the heart rate. The rate augments during the precrisis stage of the low oxygen test, at first slowly and then more rapidly. This is the observation of fact

previously well established as a typical compensatory response of the heart during the official altitude test.

The so-called sinus arrhythmia, present in most individuals, is accentuated during the early period of the altitude test in many. This fact makes it difficult to select at random individual pulses in any two periods under comparison that represent exactly the same phase in the sinus variations. On the whole, the cycles measured vary in fair agreement with the clinical increases in rate noted in the radial counts by twenty second intervals.

The oxygen left in the rebreather was determined at the close of each test. In the graphs the terminal oxygen percentage is recorded over the minute at which the test was closed. On the assumption that oxygen consumption was constant minute by minute, a straight line is drawn from the point on the chart at the beginning of the test at 21 per cent. oxygen to the point in the scale representing the terminal percentage at the time of the close of the test. This is the practice in recording the Air Service tests. The percentage of oxygen at any minute in the test can be read off directly from the chart. This method of reading is the one used in determining the oxygen of the air breathed at the various intervals at which cardiograms are shown in the plates.

#### PROTOCOLS OF OBSERVATIONS CONNOTING TERMINAL HEART FAILURE OF VARIOUS TYPES

PROTOCOL 1.—Sgt. H. B. D.; oxygen reached 6.7 per cent.; time, 27 minutes, 20 seconds.

The physiologic and clinical responses recorded minute by minute through the entire test are presented in Figure 1. The chart shows very good compensations through to the end of the twenty-sixth minute. During the twenty-seventh minute, the systolic blood pressure fell sharply from 152 to 126 mm., and to 111 mm. at the first blood pressure reading after the experiment. In the interim, the systolic pressure had been lower, as indicated by the further rise of pressure to 134 mm. on the third reading of the recovery.

The heart gave a fine compensatory increase of rate to the twenty-seventh minute. The clinical chart indicates a gradual and normal return to the pre-experiment level. However, the electrocardiogram taken after the twenty-seventh minute and just before the close of the test, shows a rate of only 70. This rate dropped to 68 at the beginning of the recovery electrocardiogram (Fig. 1, E-R). This electrocardiographic rate occurred between the last clinical test and the first recovery rate recorded. The true curve, therefore, shows a sharp fall, to the marks E-R, and then a rise of 22 mm. to the clinical recovery rate. It is assumed that the fall in systolic blood pressure and in heart rate are, in fact, simultaneous although recorded in sequence.

The respiratory minute volume varied greatly, between 54 and 81 deciliters per minute to the twenty-third minute, an average between 65 and 70. During the last three minutes, the volume ran up to 103 deciliters, which in itself is good but not full compensation for the reduction of oxygen below 7 per cent.

During the first seven records, including the twenty-fourth minute, the electrocardiograms show the typical variations. There was a decided sinus arrhythmia. The extreme rates during the arrhythmia are indicated by the

pairs of measurements in the tenth, fifteenth, twentieth, twenty-second and twenty-fourth minutes. In the twentieth minute, oxygen 10.5 per cent., the sinus arrhythmia varied from 0.548 to 0.784 second per single beat, i. e., theoretical rates of 110 and 76 beats per minute. These variations occur within the time between the sixth and sixteenth beats.

During the extreme changes in rate there is little change in the P-R interval, a maximum variation of 0.008 second in this case. On the other hand, the R-T shortens with the acceleration of rate, i. e., as the oxygen decreases. Apparently, it is the oxygen factor that is involved, since in the shorter beat

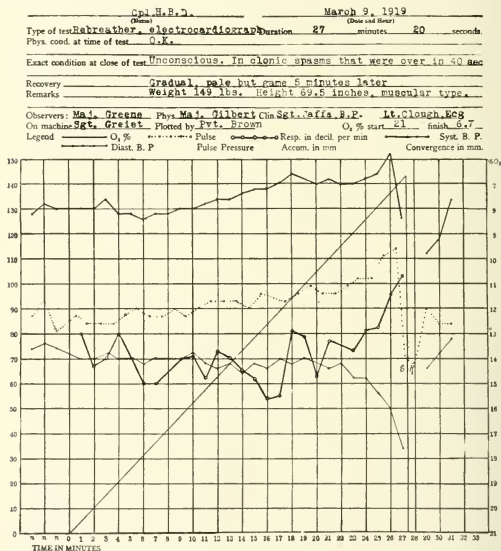


Fig. 1.—The clinical charts show the percentage of oxygen in the air breathed, oblique line; the heart rate, dotted line; systolic blood pressure, the top line; the diastolic blood pressure, the bottom line; and the volume per minute of air breathed, heavy line. E. R., the rate computed from the electrocardiographic record at the moment the test was closed and 20 seconds later. The long spaced stipples indicate the heart rate shifts between the pre- and post-clinical rates as determined by the electrocardiogram. The blood pressures in mm. mercury, heart rates per minute, and deciliters of air per minute are indicated in the legend to the left; the percentage of oxygen to the right. This legend answers for Figures 1 to 7, inclusive.

given for the normal, 0.628 second, the R-T interval is 0.320 second, whereas in the twentieth minute the pulse of 0.784 second duration shows an R-T interval of 0.300 second.

In the energy of the deflections, the P wave is comparatively constant. The negative Q, which is present in this case, is relatively constant though it decreases with the onset of low oxygen. The R also decreases in amplitude. The S varies through a wide range. The T is diminished by at least half and is somewhat lower in the pulses of shortest duration.

When the test reached 6.8 per cent. oxygen in the twenty-seventh minute, decided changes occurred in the character of the electrocardiogram which are of greatest importance in tracing the onset of cardiac collapse. They did not

TABLE 1.—SGT. H. B. D., MARCH 9, 1919

Time of run 27 minutes 20 seconds. Final oxygen, 6.7 per cent.

Trace and Pulse No.	Time	Oxygen, per Cent.	Duration in Sec.			Amplitude in Mm.					Remarks
			R-R	P-R	R-T	P	Q	R	S	T	
1-5	Normal	21.0	0.828	0.140	0.320	1.5	2.0	16.0	4.0	3.5	Sinus arrhythmia shown by variation of R-R Arrhythmia slow and marked
1-21	Normal	21.0	0.628	0.140	0.320	2.0	2.0	16.0	2.0	4.0	
2-1	5 min.	18.4	0.540	0.140	0.320	1.8	2.0	14.0	2.5	2.5	
3-1	10 min.	15.7	0.800	0.140	0.320	1.4	1.2	15.0	3.0	2.8	
3-7	10 min.	15.7	0.612	0.144	0.320	1.6	1.4	13.0	2.0	2.4	Long period arrhythmia
4-5	15 min.	13.1	0.776	0.144	0.300	4.6	1.0	15.5	4.0	2.0	
4-1	15 min.	13.1	0.560	0.136	0.312	2.0	2.0	14.0	3.0	2.2	
5-6	20 min.	10.5	0.784	0.144	0.300	1.6	1.3	16.5	4.5	2.0	
5-16	20 min.	10.5	0.548	0.136	0.292	1.6	1.0	13.0	2.0	1.8	Sinus arrhythmia
6-6	22 min.	9.5	0.760	0.136	0.300	1.5	1.0	16.0	4.0	2.0	
6-16	22 min.	9.5	0.520	0.144	0.292	2.0	1.4	12.5	2.0	1.8	
7-1	24 min.	8.4	0.648	0.144	0.300	1.8	1.3	14.5	3.0	2.0	
7-7	24 min.	8.4	0.504	0.136	0.304	1.8	1.2	13.0	2.5	2.0	Colonic spasms at end of Experiment P not evident
8-1	26 min.	7.4	0.540	0.140	0.296	1.0	1.6	13.0	4.0	2.2	
9-1	27 min.	6.8	0.760	none	0.300	none	2.0	16.0	1.0	3.0	
10-2	Recovery	21.0	0.868	none	0.320	none	2.0	18.0	2.0	3.4	
10-3	Recovery	21.0	0.832	none	0.320	none	1.6	15.0	2.0	3.2	
10-4	Recovery	21.0	0.812	none	0.320	none	1.6	16.0	2.0	3.0	
10-5	Recovery	21.0	0.760	0.064	0.320	1.2	0.0	17.0	2.0	3.2	
10-6	Recovery	21.0	0.760	0.128	0.320	2.0	1.2	14.5	2.5	3.6	
10-7	Recovery	21.0	0.700	0.144	0.328	2.0	1.0	14.0	2.5	4.0	
10-8	Recovery	21.0	0.560	0.140	0.320	2.0	1.0	14.0	3.4	4.2	
10-9	Recovery	21.0	0.640	0.144	0.320	1.8	0.6	14.0	3.0	4.0	
10-10	Recovery	21.0	0.888	0.140	0.320	2.0	0.6	13.5	3.0	4.0	
10-19	Recovery	21.0	0.872	0.128	0.320	1.6	1.0	15.0	3.0	4.5	

come on until the approach of unconsciousness which was coupled in this man with intense clonic muscular spasms at the close of the test. These clonic spasms are in themselves of special significance since the man was a vigorous neuromuscular type and in the best of physical condition.

A short cardiogram was obtained just before the experiment ended. The heart rate had slowed down to between 75 and 80 per minute from a previous rate of 111 in the twenty-sixth minute. The ventricular complexes are of the normal type. Although the presence of extraneous currents from the clonus destroyed the regularity of the record no P wave could be detected. It is apparent that in the unrecorded interval, the P wave had dropped out. In other words, the sino-auricular pacemaker no longer gave evidence of functioning. The normal type of ventricular complex shows that the auriculoventricular pacemaker controlled this rhythm. This is a case of suppression of the sino-auricular beat, similar to Lewis' experiment on the cat heart. An alter-

native hypothesis would assume that the P wave is buried in some part of the R-S-T complex, but the ventricular complex is like the normal in amplitude and duration. A careful comparison with the earlier normals gives no suggestion of a superimposed P wave occurring in any portion of the ventricular complex, although this does not preclude the possibility of such an inclusion. If we assume that the P is completely suppressed, then we would have at the same time to accept the deduction that reversed conduction from the A-V node is also suppressed. This point cannot be proven from this particular test, but a suppression of conduction does seem to occur in the test of Cpl. F. J. D. in whom there is dissociation of auricular and ventricular rhythms (Table 2).

In the after period the first three ventricular complexes are not associated with P waves. In the fourth contraction, there is a P wave with a P-R interval of 0.060 second. Table 1 presents the series of measurements for the first ten contractions and the nineteenth or last of the series. In the first, second and third, there is no evidence of an auricular contraction. In the fourth beat, the P wave appears 0.064 second in advance of the R wave. In the fifth it is 0.128 second, and in the succeeding sixth to the eighteenth beats the intervals are again normal, 0.140 second. During this series the ventricular complex is normal in type. It is constant in duration, namely 0.320 second. A rather striking point is the acceleration of the rate with the reappearance of sino-auricular control of the contraction. The rate accelerates through the equivalents of 68, 69, 72, 74, 81, 81, 86, 95, 94; then slows to 68, 71, 68, 68, 68, 70, 70, 69, 69, during the reestablishment of the normal relations. Progressive and gradual recovery of the pace-making function in the ascending direction is indicated. During the suppression of the P wave, the origin of the beat is in the A-V nodal tissue. In the fourth and fifth beats, it is higher up, and on and after the sixth beat it apparently occurs in the S-A node, as indicated by the normal conduction time. The slower rate introduced at the tenth beat is indicative of returning vagal tonic control of the rhythm.

TABLE 2.—F. J. D., APRIL 9, 1919

Time of run 24 minutes, 26 seconds. Final oxygen, 8.1 per cent.

Trace and Pulse No.	Time	Oxygen, per Cent.	Duration in Seconds				Amplitude in Mm.				
			P-P	R-R	P-R	R-T	P	Q	R	S	T
1-1	Normal	21.0	0.920	0.920	0.344	0.344	1.3	none	10.0	2.5	+0.6 to -0.2*
2-2	5 min.	18.4	0.838	0.824	0.308	0.360	1.5	none	9.6	2.0	+0.7 to -0.6
3-2	10 min.	15.8	0.800	0.804	0.320	0.360	1.4	0.3	9.4	2.0	+0.6 to -0.7
4-6	15 min.	13.1	0.748	0.744	0.316	0.344	1.6	0.3	9.0	3.0	+0.6 to -0.4
5-1	20 min.	10.5	0.800	0.792	0.296	0.328	1.2	0.8	9.2	3.0	+0.2 to -0.8
6-2	22 min.	9.4	0.728	0.716	0.296	0.336	1.8	0.4	9.0	3.2	+0.6 to -0.8†
7-1	24 min. "off"	8.1	0.680	0.680	0.308	0.336	1.0	trace	9.0	3.0	+0.7 to -0.2
8	Last pulse	21.0	0.712	0.712	0.314	0.342	2.0	none	9.0	3.0	-0.2 to -tr.
7-1	Five successive	8.1	0.680	0.680	0.308	0.336	1.0	trace	9.0	3.0	+0.7 to -0.2
7-2	pulses in	8.1	0.728	0.680	0.288	0.344	1.5	0.1	9.0	3.0	+0.8
7-3	the 24th	8.1	0.784	0.692	0.212	0.320	1.5	trace	8.0	2.4	+0.6
7-4	minute	8.1	0.896	0.716	0.112	0.320	1.6	trace	8.0	3.0	+0.4
7-5		8.1	0.960	0.740	0.048‡	0.340	1.6	none	8.0	3.0	+1.2

\* T = di-phasic, in some pulses, +0.6 to -0.4 and more.

† Complete block developed. See Table 5. T = di-phasic.

‡ R-P interval.

Protocol 2.—Cpl. F. J. D.; oxygen 8.1 per cent.; time 24 minutes, 26 seconds.

The clinical sheet of Cpl. F. J. D. shows compensations of the circulatory system to 10 per cent. oxygen (Fig. 2). The normal heart rate of 63 was augmented to 96 during the twenty-second minute, then fell sharply during the twenty-third and twenty-fourth minutes. The systolic blood pressure was sustained to the end of the experiment, but diastolic pressure broke at twenty-

one minutes. The electrocardiogram in the twenty-fourth minute shows the onset of complete heart block. This is coupled with a slow ventricular rate. It is interesting that the systolic pressure was maintained for a few moments in the presence of both slow heart rate and sharp diastolic break. There was complete failure of compensation in respiration. The very large minute volume of air breathed in the sixth and seventh minutes was due to a series of deep sighing inspirations. In fact, the whole respiratory record was extremely irregular in tidal volume.

Cpl. F. J. D. March 9, 1919  
(Name) (Date and Hour)  
Type of test: Rebreather, Electrocardiogram, Duration .24 minutes 26 seconds.  
Phys. cond. at time of test: O.K. but clinical history of heart block  
Exact condition at close of test: Very cyanotic but conscious  
Recovery: Revived instantly  
Remarks: Respirations vary extremely in depth  
Weight 150 lbs. Height 70 inches  
Observers: Maj. Greene Phys. Maj. Gilbert Clin. Sgt. Greist, S. P. Lt. Clough, S. P.  
On machine: Sgt. Jaffa Plotted by: Pvt. Brown O<sub>2</sub>% start 21 finish 8.1  
Legend: — O<sub>2</sub>% ..... Pulse —○— Resp. in decil. per min. — Syst. B. P.  
— Diast. D. P. — Pulse Pressure — Accom in mm. — Convergence in mm.

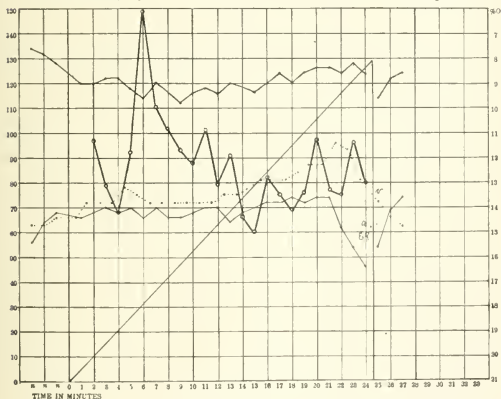


Figure 2

Eight electrocardiograms were secured. Only slight changes in the form of the cardiogram occurred during the first twenty-two minutes. There was a shortening of the P-R time associated with the increase in heart rate. The normal time of contraction was 0.920 second, in the twenty-second minute, the last contraction of Figure 6, Plate I, the time of the beat was 0.716 second. Little change occurred in the time of the ventricular complex. The conduction time was exceptionally long, 0.344 second in the normal tracing, which is two and one-half times the normal average.

No striking changes occurred in the amplitudes of the different deflections. However, the entire series of records show diphasic T. waves. In some portions a distinct U wave also occurred (Plate I, Fig. 1, also in Fig. 3). The long conduction time is suggestive of some possible lesion in the conducting tissue, with corresponding delay in the process.

In the twenty-fourth minute a change occurred in the rhythm which admits of some discussion. The entire record secured at 8.1 per cent. is presented in Figures 7 and 8, Plate I. Inspection of this record shows that complete dissociation occurred. The first P-R interval of the record is slightly less than the normal for the individual, and each succeeding interval is decreased in time. At the same time, there is lengthening of the P-P interval, evidencing auricular slowing, while the R-R interval remains substantially the same, or does not increase in proportion. Two possibilities are suggested: first, that in the preceding unrecorded interval, conductivity had depressed, and that the dissociation is due to a final complete internodal block. Second, that the dissociation is due to the depression of the pace-making function of the sino-auricular node to a point below the rate of stimulus production inherent in the A-V node at that time, allowing the A-V node to assume the dominant rhythm. Independent rhythm cannot be induced by this second process, except when reverse block is present.

TABLE 3.—CPL. F. J. D. TWENTY-FOURTH MINUTE. OXYGEN 8.1 PER CENT.

Giving the auricular intervals, P-P, and the ventriculars, R-R, and the time from the beginning of the auricular complex to the next succeeding ventricular complex. The series includes all the beats during the twenty-fourth minute, i. e., from the beginning of complete block to the end of the test. The block appeared at 8.1 per cent. oxygen.

Ventricular Contraction Serial No.	Intervals in Seconds			Computed Rates	
	P-P	R-R	P-R	Auricular	Ventricular
1.....	0.680	0.680	0.28	88	88
2.....	0.728	0.680	0.26	82	88
3.....	0.784	0.692	0.20	76	87
4.....	0.896	0.716	0.10	67	84
5.....	.....	0.740	.....	.....	81
6.....	0.960	0.644	0.64	62	93
7.....	0.936	0.768	0.36	64	78
8.....	0.984	0.800	0.21	61	75
9.....	0.920	0.808	0.00	65	75
10.....	.....	0.804	.....	.....	75
11.....	0.880	0.898	0.74	68	67
12.....	0.880	0.808	0.68	68	75
13.....	0.880	0.820	0.60	68	97
14.....	0.824	0.748	0.34	73	80
15.....	0.856	0.748	0.24	73	82
16.....	0.920	0.732	0.12	65	82
17.....	.....	0.732	.....	.....	82
18.....	0.840	0.732	0.68	71	82
19.....	0.860	0.616	0.52	70	97
20.....	0.760	0.696	0.32	79	86
21.....	0.740	0.700	0.22	81	86
22.....	0.800	0.692	0.20	75	86
23.....	0.940	0.704	0.05	64	85
24.....	.....	0.720	.....	.....	83
25.....	0.920	0.664	0.56	65	90
26.....	0.960	0.716	0.30	63	84

Whatever its etiology, dissociation clearly occurs. In this record the P wave is seen to move through the ventricular complex four times which argues against A-V control of the auricular rhythm. Table 3 shows a record of the measurements for the entire tracing. The recovery tracing (Plate I, Fig. 9) shows that the normal relationship has returned as regards the sequence. We feel that a depression of the rhythmicity of the sino-auricular node is definitely shown. In itself the record is insufficient wholly to justify this conclusion. But when compared with suppression of rhythm in the auricles of other hearts

to be described later, and with the added evidence that in routine Air Service examinations a decrease in rate was frequently observed in acute oxygen want, we feel that our conclusion is warranted.

PROTOCOL 3.—Pvt. J. F.; final oxygen, 8.4 per cent.; total time, 21 minutes, 56 seconds.

The clinical chart is of peculiar interest as a type showing sudden collapse at a comparatively high percent. of oxygen, between 9 and 10 per cent. There is a clinical history diagnosed as effort syndrome. The blood pressures, both systolic and diastolic, steadily fell to 9.5 per cent. oxygen when collapse began.

Pvt. J. F.		March 10, 1919	
(Name)		(Date and Hour)	
Type of test	Rebr.	Electrocardiograph	Duration 21 minutes 56 seconds
Phys. cond. at time of test O.K.			
Exact condition at close of test: Very cyanotic, spoke in 15 seconds			
Recovery Prompt			
Remarks: Weight 132 lbs. Height 68 inches, convalescent N.C.A.			
Observers:	W. J. Greene	Phys. W. J. Gilbert	Clin. Sgt. Graist, BB
On machine:	Sgt. Jaffa	Plotted by	Pvt. Brown
Legend		O <sub>2</sub> % start 21 finish 8.4	
— Diast. D. P.		— Pulse	— Resp. in decil. per. min.
		— Pulse Pressure	— Syst. B. P.
			— Convergence in mm.

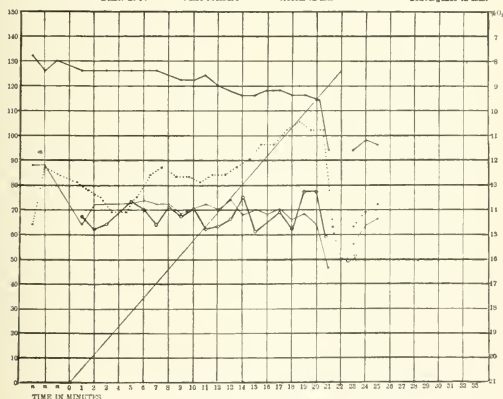


Figure 3

There was no respiratory compensation during the entire run. The heart rate increased from a normal of 69 to a maximal of 105 in the nineteenth minute. In the last minute the rate fell from 102 to 63 at the last clinical count. The electrocardiogram of the twenty-first minute gives a rate of 68 (Plate 2, Fig. 6). In the electrocardiogram in the early recovery stage and just before the first clinical recovery record, the heart had slowed to an equivalent rate of 50 in the 4th beat (E. R., Plate 2, Figs. 3 and 7). The clinical record shows the lack of compensatory elasticity in the effort syndrome type. The test was not



carried to the complete limit of endurance. The usual changes in the electrocardiogram with reduced oxygen appear only in the T wave. The P-R and R-T intervals are constant.

The chief interest in this test lies in the sudden reduction of heart rate in the twenty-first minute. The slow rate continued throughout the recovery record with pure air. The electrocardiogram is normal in form although the heart rate was reduced to 68 per minute just before the experiment ended, and to 50 per minute during the early recovery. The sudden slowing of the rate just at the close of the experiment is a typical instance of the effect of oxygen want in slowing stimulus production at the crisis.

TABLE 4.—Pvt. J. F., MARCH 10, 1919

Time of run 21 minutes, 36 seconds. Final oxygen, 8.4 per cent.

Trace and Pulse No.	Time	Oxygen, per Cent.	Duration in Sec.			Amplitude in Mm.					Remarks
			R-R	P-R	R-T	P	Q	R	S	T	
1-2	Normal	21.0	0.668	0.140	0.306	1.4	none	9.0	0.7	4.0	Effort syndrome ease
2-2	5 min.	18.1	0.760	0.144	0.308	1.0	none	9.5	1.0	2.8	
3-4	10 min.	15.3	0.700	0.148	0.304	1.0	none	9.0	1.0	3.0	Slight sinus arrhythmia
4-2	15 min.	12.4	0.616	0.144	0.296	1.4	none	9.0	0.6	2.4	
5-2	20 min.	9.5	0.560	0.140	0.292	1.4	none	10.5	0.4	1.6	Failing heart
6-4	21 min.	8.9	1.052	0.144	0.300	1.6	none	10.5	none	2.5	
7-2	Recovery	21.0	1.104	0.144	0.320	1.0	none	10.5	none	3.4	Spoke within 15 secs.

There were signs of approaching unconsciousness at the moment of ending the experiment, but F. spoke fifteen seconds after beginning to breathe pure air.

PROTOCOL 4.—Pfc. T. H. K.; final oxygen, 7.1 per cent.; total time, 27 minutes, 9 seconds.

The clinical interest is in the partial collapse of the heart and fall of blood pressure without definite loss of consciousness. T. H. K. was a strong muscular type and was taken off because of beginning general clonic tremors. Muscular clonics lasted for 20 seconds, but he recovered control after the first few inspirations.

TABLE 5.—Pfc. T. H. K., MARCH 9, 1919

Time of run 27 minutes, 9 seconds. Final oxygen, 7.15 per cent.

Trace and Pulse No.	Time	Oxygen, per Cent.	Duration in Sec.			Amplitude in Mm.					Remarks
			R-R	P-R	R-T	P	Q	R	S	T	
1-7	Normal	21.0	0.840	0.160	0.340	1.0	none	16.0	none	3.0	Trembling Sinus arrhythmia
2-5	5 min.	18.4	0.808	0.168	0.360	1.0	none	16.5	none	3.5	
2-1	5 min.	18.4	0.760	0.168	0.352	1.2	none	16.5	none	3.0	Sinus arrhythmia
3-2	10 min.	15.9	0.696	0.168	0.332	1.6	none	15.5	none	2.4	
4-2	15 min.	13.9	0.748	0.160	0.336	1.0	none	15.0	none	2.0	
4-6	15 min.	13.3	0.672	0.160	0.336	1.3	none	16.0	none	2.0	
5-2	20 min.	10.7	0.640	0.160	0.320	1.5	none	16.0	none	1.8	T very flat
6-2	22 min.	9.7	0.576	0.152	0.300	1.6	none	16.0	none	1.6	
7-2	24 min.	8.7	0.544	0.160	0.312	1.5	1.4	17.0	none	0.4±	
8-7	26 min.	7.7	0.548	0.148	0.300	1.5	2.0	16.0	none	0.4±	
9	Recovery*										

\* See Table 6.

The systolic blood pressure remains constant to 8.2 per cent. oxygen, then drops suddenly and rapidly. The diastolic pressure also remains constant at 80 mm. to 9.7 per cent., then rapidly falls through five minutes to 44 mm. The heart rate of 80 per minute increased to 90 at the twenty-ninth minute then to 116 at the last reading. The electrocardiograms show that the rate

dropped through 63 to 55 and became very irregular (Plate 3, Figs. 9 and 10) during the interval between the last clinical pulse reading and the first recovery reading.

There were only slight changes in the electrocardiogram to the twenty-sixth minute. No important change in the conduction, and only very slight shortening of the R-T interval occurred as the usual augmentation of rate came on. A long tracing of thirty-two heart beats taken at the close of the

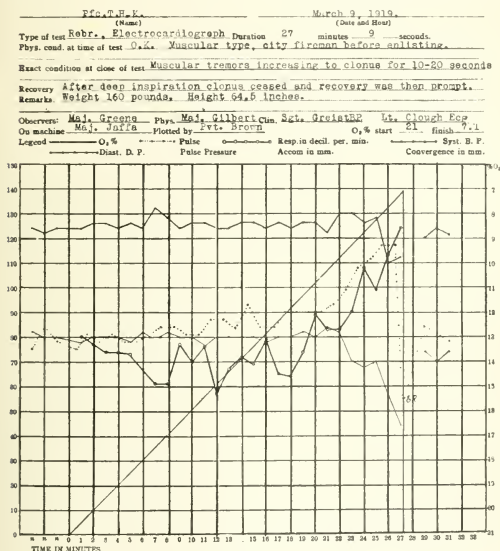


Figure 4

experiment and during the early recovery stage shows complete dissociation of the auricular and ventricular rhythms. Already at 7.7 per cent. oxygen the rate had slowed, though the sequence was still normal. In the unphotographed interval the pace making function of the S-A node slowed below the critical point of stimulus production in the A-V node and the nodes became independent. This is shown by the irregularity of the P-P interval, where it can be determined, and by the evidence of varying locus of stimulus production in the auricle as evidenced by both direct and inverted form and varying amplitudes of the P waves. In addition, we have the increase of cardiac muscle irritability as shown by two heterogenetic ventricular beats. In fact, this fea-

ture of the record suggests that of digitalis poisoning, or the type of hyper-irritability observed in the electrocardiograms of experimental animals after chloroform.

TABLE 6.—PFC. T. H. K., MARCH 9, 1919

Time of run 27 minutes, 9 seconds. Final oxygen, 7.15 per cent.  
Electrocardiogram, No. 9, taken during the early after or recovery period. No S wave during this record.

Pulse	Duration in Seconds				Amplitude in Mm.			Remarks
	R-R	P-R	R-T	P	Q	R	T	
1	0.952	0.500	0.360	-2.0	none	18.0	3.4	
2	0.528	0.620	0.340	-2.0	none	19.0	3.0	
3	0.940	0.200	0.328	-1.6	0.5	18.0	2.5	
4	0.944	0.100	0.340	-2.0	0.5	18.5	1.5	
5	0.944	0.340	0.360	+0.5	1.5	19.0	2.0	
6	0.752	none	0.360	none	0.5	20.0	2.0	
7	0.940	0.180	0.320	+1.2	0.5	19.0	1.8	
8	0.504	none	0.360	none	1.0	20.0	2.0	
9	0.940	0.240	0.320	+2.0	none	18.5	3.2	
10	0.908	none	0.360	none	1.0	18.5	3.2	
11	0.944	-0.144*	0.340	none	1.0	18.5	2.0	* R-P
12	0.528	none	0.320	none	1.0	18.0	0.5	
13	0.900	0.220	0.320	-1.0	none	17.0	2.0	
14	0.960	-0.650	0.360	-2.0	none	20.0	3.0	
15	0.484	none	0.360	none	none	19.0	2.0	-P superimposed on
16	0.928	0.240	0.320	+1.8	none	16.5	2.6	the lower limb of R
17	0.512	none	0.380	none	none	19.0	4.5	
18	0.948	0.240	0.320	P+T	none	17.0	2.0	Combined +P and T
19	0.480	none	0.360	none	0.5	19.0	3.5	
20	0.920	0.240	0.380	-1.5	none	10.0	?	Ventricle complex ec-
21	0.480	none	0.372	none	0.5	18.5	3.0	tropic
22	0.824	0.320	0.380	?	none	10.0	3.0	
23	1.080	0.664	0.348	+1.0	none	17.0	3.0	
24	0.972	0.050	0.360	+1.0	none	19.0	2.5	
25	0.472	none	0.360	none	none	19.0	3.0	
26	0.920	0.280	0.336	-1	none	10.0	4.0	
27	1.000	0.160	0.360	+1	none	18.0	2.0	
28	1.000	-0.160	0.360	+1	1	19.0	2.0	
29	0.488	none	0.360	none	none	18.5	2.8	
30	0.928	0.220	0.320	+	none	16.5	2.5	
31	1.012	0.140	0.360	+1	1	17.5	2.5	
32	.....	-0.140	0.360	+1	none	16.0	2.2	

The physiologic and clinical chart is unique in several features. He reached 5.9 per cent. oxygen, an equivalent altitude of 31,500 feet. He made good compensations but not in the typical way. Instead of the usual early gradual cardiac acceleration beginning about the fifteenth minute, his heart rate ran very uniform until the last two minutes. The rate then augmented from 84 in the twenty-second to 150 in the twenty-fourth minute just before the close. The systolic pressure was over 150 mm. from the start but remained constant to the twelfth minute. From this time it increased steadily for eight minutes then sharply the last two minutes to a total of 194 mm. The diastolic pressure slowly increased until the very last minute when it suddenly broke 20 mm.

The effect of prolonged athletic activity is manifest in Sgt. M.'s excessive respiratory minute volume. This began at 17 liters in the first minute, dropped to just under 10 liters at 10 minutes, and increased rapidly after the seventeenth minute to the enormous volume of 26.8 liters during the twenty-third or last full minute. Compensations are due to augmentation of respiratory volume and of blood pressure. These meet the strain to 7 per cent. oxygen, when cardiac acceleration was added. At the moment of unconsciousness the break in diastolic pressure and in respiration had begun.

W. C. M. was physical director at Lakewood. He is a man of exceptional muscular development and physical endurance. There was a lively competition among the men at Lakewood in an attempt to exceed the record of Sgt. M. and the sergeant himself entered into the spirit of this competition. Notwithstanding the large volume of air breathed, he became very cyanotic during the last five minutes. The clinician did not terminate the test until the onset

of unconsciousness when the mouthpiece was instantly removed. Consciousness reappeared after the first inhalation of pure air. Reflex muscular control was not lost and the sergeant protested that he had not yet reached his limit.

The heart rate was very constant and the cardiograms show that there was no change in the P-R interval until the twentieth minute, and then only in the shorter beats of the arrhythmia periods. The R-T intervals became shorter

PROTOCOL 5.—Sgt. W. C. M.; final oxygen, 5.9 per cent.; total time, 23 minutes, 48 seconds.

Sgt. W. C. M.		March 26, 1919	
(Name)		(Date and Hour)	
Type of test	Rebr., Electrocardiograph		
Phys. cond. at time of test	O.E. Physical director	Duration	23 minutes 48 seconds.
Exact condition at close of test: <u>Momentary unconsciousness, no loss of muscular control</u>			
Recovery	Immediate		
Remarks	Weight 212 lbs. Height 74 inches		
Observers:	Maj. Greene	Phys. Maj. Gilbert	Clin. Sgt. Jaffa, D. P.
On machine:	Sgt. Greist	Plotted by Pvt. Brown	Lt. Clough, Sgt.
Legend	O <sub>2</sub> % ——— Pulse ——— O <sub>2</sub> resp. in decil. per min. ——— Syst. B. P. ——— ——— Diast. D. P. ——— Pulse Pressure ——— Accou. in mm. ——— Convergence in mm.		
			O <sub>2</sub> % start 21 finish 5.9
			Accou. in mm. 205

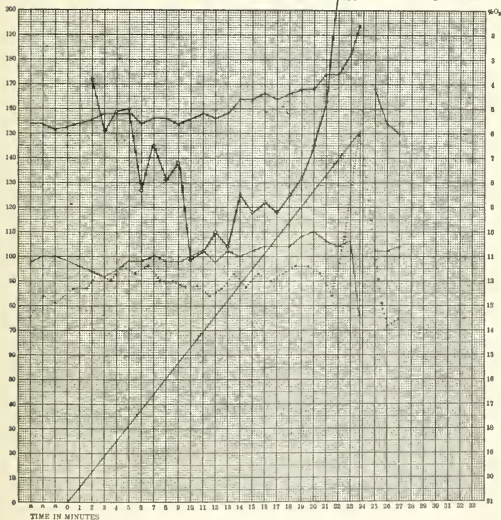


Figure 5

beginning at the twentieth minute. The character of the electrocardiogram was abnormal in only one feature. The R wave was short and bifurcated. The U wave was present in many of the cycles.

TABLE 7.—SGT. W. C. M., MARCH 10, 1919

Time of run 23 minutes, 48 seconds.

Final oxygen, 5.9 per cent.

Trace and Pulse No.	Time	Oxygen, per Cent.	Duration in Sec.			Amplitude in Mm.					Remarks
			R-R	P-R	R-T	P	Q	R	S	T	
1-1	Normal	21.0	0.812	0.160	0.320	1.5	none	7.0	none	2.0	Some sinus arrhythmia Some sinus arrhythmia
2-2	5 min.	17.8	0.580	0.160	0.320	1.0	tr.	7.5	none	1.2	
3-1	10 min.	14.6	0.680	0.160	0.320	1.0	none	7.5	none	1.2	
4-2	15 min.	11.5	0.680	0.160	0.320	0.8	none	7.5	none	1.0	
5a-1	20 min.	8.3	0.656	0.160	0.312	0.8	0.6	7.0	none	1.0	
5b-3	20 min.	8.3	0.632	0.144	0.300	0.8	1.0	6.5	none	1.0	
6-1	22 min.	7.0	0.504	0.160	0.260	1.2	1.0	9.0	none	1.0	
2d from last	22 min.	7.0	0.468	0.136	0.256	1.0	2.0	7.0	none	0.6	
7-3	Recovery	21.0	0.700	0.144	0.300	1.0	1.0	7.0	none	1.6	Momentary unconsciousness
Last pulse	Recovery	21.0	0.740	0.160	0.292	0.6	1.0	8.0	none	2.0	

The stress of oxygen want on local cardiac mechanisms appears only in the recovery tracing which was taken at practically the moment of the removal of the mouthpiece (Plate 4, Fig. 8). The fifth beat in this figure shows a very slight negative P wave, the sixth beat has a well defined negative P. The inverted P continues through seven successive contractions. On the eighth, i. e., the twelfth beat of the figure, the negative wave is reduced in amount, and on the next beat the normal positive P appears and continues until the end of the photograph. During the period of inverted P waves the rate is reduced slightly as compared with the rate preceding and following the group, i. e., from 167 to 157, then back to 166 per minute. We consider this a splendid example of just beginning displacement of origin of the sino-auricular rhythm. The point of origin of the rhythm is evidently from a new source below, or from a lower point in the normal pace making center. It is the initial stage of the effect of oxygen want as affecting the reactions of the heart, in which the most advanced stages are represented by the terminal electrocardiograms of T. B. M. and D. W. O.

Protocol 6.—Sgt. T. B. M.; final oxygen, 7.6 per cent.; total time, 25 minutes, 54 seconds.

Sergeant T. B. M.'s physiologic and clinical chart shows poor compensations. His slow heart-rate in the late electrocardiograms is explained by the clinical collapse during the last two minutes of his test. The heart increased in rate beginning on the tenth minute and the increase amounts to about 25 beats during the last five minutes. It ends in an abrupt drop from a rate of 117 to 75 in the last minute. The electrocardiogram (Plate 5, Fig. 8), taken during the twenty-fifth minute (apparently later in the minute than the clinical rates recorded) shows the new slow rate, which had fallen to 62 per minute in the first beat photographed. In the early recovery period the rate varied from 61 to 64 and was fairly constant.

Although unconscious at the last, it is obvious that the heart rate was in itself adequate. The failure in compensation was due to the inadequate blood pressure. Both systolic and diastolic pressures fell from the beginning, but the fall was marked and more rapid after the eighteenth minute as the chart shows. Respiration also failed of adequate compensation. The highest minute

Sgt. T. B. M. March 10, 1919  
 (Name) (Date and Hour)  
 Type of test: Rebr., Electrocardiograph Duration 25 minutes 54 seconds.  
 Phys. cond. at time of test: O.K.  
 Exact condition at close of test: Unconscious, neck muscles relaxed, pale.  
 Recovery: Breathing slow and faint.  
 Remarks: Slow and gradual, breathing normal 26 sec., talked 96 sec.  
 Pale and perspiring 5 minutes later.  
 Weight 136 lbs., height 67 inches.  
 Observers: Maj. Greene Phys. Maj. Gilbert Clin. Sgt. Greist, B.P. Lt. Clough, Ecg  
 On machine: Sgt. Jaffe Plotted by: Pte. Brown O<sub>2</sub> % start 21 finish 7.6  
 Legend: — O<sub>2</sub> % ..... Pulse ○—○—○ Resp. in decil. per. min. — Syst. B. P.  
 — Diast. D. P. — Pulse Pressure — Accom. in mm. — Convergence in mm.

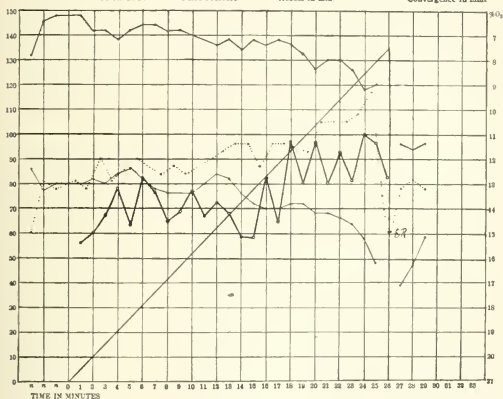


Figure 6

TABLE 8.—SGT. T. B. M., MARCH 11, 1919

Time of run 25 minutes, 54 seconds.

Final oxygen, 7.6 per cent

Trace and Pulse No.	Time	Oxygen, per Cent.	Duration in Seconds			Amplitude in Mm.				
			R-R	P-R	R-T	P	Q	R	S	T
1-1	Normal	21.0	0.832	0.140	0.340	1.0	1.0	18.5	2.5	3.2
2-1	5 min.	18.4	0.760	0.132	0.328	1.0	1.0	19.0	2.5	2.0
3-1	10 min.	15.9	0.652	0.144	0.320	1.0	1.0	19.0	3.0	1.5
3-11	10 min.	15.9	0.840	0.140	0.320	1.0	1.0	20.0	2.5	2.5
4-10	15 min.	13.3	0.520	0.132	0.280	2.0	1.5	19.0	1.0	1.5
4-1	15 min.	13.3	0.672	0.140	0.340	1.4	2.0	20.0	2.0	1.4
5-4	20 min.	10.7	0.520	0.132	0.308	1.3	1.0	18.0	2.0	1.0
5-11	20 min.	10.7	0.606	0.148	0.280	1.0	1.0	20.0	2.0	1.0
6-15	22 min.	9.6	0.604	0.128	0.312	2.0	2.5	19.0	3.0	1.0
6-1	22 min.	9.6	0.628	0.136	0.300	2.0	1.5	21.0	3.0	1.0
7-5	24 min.	8.6	0.472	0.120	0.272	1.5	1.0	18.0	2.0	0.4
7-1	24 min.	8.6	0.512	0.132	0.320	2.0	2.0	19.0	2.5	0.5
8-1	25 min.	8.1	0.944	none	0.330	none	1.4	19.0	2.0	2.0
9-1	Recovery	21.0	0.920	0.092	0.348	1.0	1.3	20.5	2.4	2.8

See Tables 9 and 10.

volume reached was only 10 liters. The whole clinical picture is that of a strong muscular type with nervous and circulatory apparatus adequate only to resist the effects of moderate reduction of oxygen. As 8 per cent. was approached, collapse of the peripheral vascular mechanism and of the heart occurred. Recovery was slow, due no doubt not so much to the heart as to the failure of the peripheral blood vessels to regain their tone, shown in the low diastolic pressure in the recovery period. Unconsciousness occurred in a few seconds short of twenty-six minutes. He recovered a degree of consciousness in twenty seconds but did not talk for one minute and ten seconds. He remained pale and perspired freely for several minutes.

The electrocardiograms show the usual progressive acceleration of pulse and decrease in the time of the cycle to the twenty-fourth minute. Conduction changed from 0.140 to 0.120 second at 8.6 per cent. oxygen. The R-T interval is also slightly decreased. Both these changes are well known functions of rate acceleration after exercise, etc. The amplitude of the deflections was constant, except for the diminution of the T wave, from 3.2 to 0.4 mm. in the twenty-fifth minute as final stage of the experiment, 8.1 per cent. oxygen.

TABLE 9.—SGT. T. B. M., MARCH 11, 1919

Time of run 25 minutes, 54 seconds.

Final oxygen, 7.6 per cent.

Trace No. 8 See Plate 5	Duration in Seconds			Amplitude in Mm.				
	R-R	P-R	R-T	P	Q	R	S	T
1	0.944	none	0.320	none	1.4	19.0	2.0	2.0
2	0.944	none	0.300	none	1.0	19.0	2.0	2.0
3	0.952	none	0.330	none	1.0	18.0	1.5	2.0
4	0.936	none	0.320	none	1.0	19.0	2.0	2.0
5	0.948	none	0.312	none	1.2	21.0	1.5	1.5
6	0.948	none	0.320	none	1.0	21.0	1.0	2.2
7	0.952	none	0.320	none	1.0	19.0	2.0	2.0
8	0.948	none	0.320	none	1.0	18.0	2.0	2.5
9	0.940	none	0.304	none	1.3	21.0	2.0	2.0
10	0.944	none	0.320	none	1.0	18.0	2.0	2.3
11	0.948	none	0.300	none	...	19.0	2.0	2.0
12	0.948	none	0.312	none	1.0	19.0	2.0	2.5
13	0.932	none	0.320	none	1.2	18.5	2.5	2.0

Profound changes occurred in the character of the terminal cardiogram, changes that do not disappear through the short recovery record obtained. The important fact is the entire disappearance of any evidence of the P wave. The loss of the P is associated with slowing of the pulse rate, from 128 to 63 per minute. In this period (Plate 5, Fig. 8) there is a record of fourteen ventricular complexes, nine of which are ideally recorded, but not one is introduced by any evidence of auricular activity. Not one of the nine is complicated by extraneous currents and all are regular and clean of type. Table 8 presents the measurements of all the complexes in Plate 5, Figure 8. The R's do not present amplitude changes that indicate inclusion of the P waves. It is evidently a rhythm of A-V nodal origin. The dissociation evidently occurred between Figures 7 and 8 of Plate 5. We have no evidence recorded in the tracings of direct auricular action, versus inhibition, the possibilities of which we have considered in relation to the cause of the dissociation.

The condition shown in the tracing at the moment before the removal of the mouthpiece and the admission of pure air (Plate 5, Fig. 8), is carried over, in part, in the tracing immediately after the admission of pure air during the recovery tracing (Plate 5, Fig. 9). The rhythm does not yet begin in the S-A node, as shown by the inverted P and the short P-R interval; the first eight contractions show an inverted P wave; no P appears during the next five contractions, and an inverted P then reappears in the last three contractions. The first eight P-R intervals are progressively shorter, from 0.092 to 0.016

second. When they reappear after five beats, they become progressively longer, from 0.040 to 0.100 second. It suggests an origin of the auricular contraction from points progressively lower in the rhythmic system, until the P either merges in the R or disappears entirely. The P then reappears, showing that the source of the rhythm moves progressively back toward the normal pace-maker. These facts show that we have a lighter degree of interference with the mechanism here than that shown in Plate 5, Figure 8. The first inhalation of pure air gave enough oxygen to partially remove the effect of oxygen want which led to the loss of rhythmicity in the normal controlling center and released activity in a lower portion of the system, as indicated by the inverted P at the beginning of the tracing. In the interval before the next inhalation of fresh air there was return of the low oxygen level which again suppressed activity in the auricle, as indicated by the total disappearance of the P wave. The progressive type of recovery in the inverse direction was produced rapidly on the influx of oxygen following the next respiration. It shows the return of the pace-maker toward its normal location. If the record could have continued during a few more heart beats it would have revealed a complete and permanent recovery of the sino-auricular control.

TABLE 10.—SGT. T. B. M., MARCH 11, 1919

Time of run 25 minutes, 54 seconds. Final oxygen, 7.6 per cent. Trace No. 9, the recovery record while breathing pure air.

Plate 5 Pulse	Duration in Seconds			Amplitude in Mm.					Remarks
	R-R	P-R	R-T	P	Q	R	S	T	
1	0.920	0.092	0.348	—1.0	1.3	20.5	2.4	2.8	
2	0.920	0.086	0.360	—1.0	1.5	19.0	2.5	3.5	
3	0.920	0.088	0.380	—1.0	1.0	20.0	1.0	3.2	
4	0.928	0.088	0.360	—1.0	1.0	23.0	1.5	3.2	
5	0.928	0.052	0.380	—1.0	1.0	21.0	1.5	3.2	
6	0.928	0.048	0.372	—0.8	?	22.0	1.0	3.0	
7	0.928	0.024	0.376	—1.0	2.0	22.0	2.0	3.2	
8	0.924	0.016	0.360	?	2.0	21.0	2.0	3.5	P and Q coincide
9*	0.928	none	0.360	none	1.6	19.0	2.0	3.5	External negative
10	0.928	none	0.360	none	1.5	20.0	2.0	3.5	wave through
11	0.936	none	0.380	none	1.5	30.5	1.2	3.0	pulses 8, 9 and 10
12	0.928	none	0.380	none	2.0	21.0	?		
13	0.928	none	0.360	none	1.8	30.5	1.0	3.4	
14	0.928	0.040	0.360	—0.8	1.0	21.0	1.0		
15	0.912	0.080	0.360	—1.2	1.0	22.0	1.5	3.0	
16	0.900	0.100	0.352	—1.0	1.5	20.0	2.0	3.0	

\* P is negative in preceding beats, and absent or buried in R-S interval here. In the thirteenth P is added to Q; in the fourteenth it is present. P is negative in entire record.

PROTOCOL 7.—Sgt. D. W. O.; final oxygen, 8.5 per cent.; total time, 25 minutes, 3 seconds.

The clinical chart of Sgt. D. W. O., Figure 7, shows that his respiratory and circulatory pre-crisis responses are noncompensating. There is a fall of diastolic blood pressure and an even systolic pressure until the critical oxygen limit is reached, then collapse occurs promptly. The initial heart rate is high and sustained with only the slightest acceleration during the test. The cardiogram taken in the last minute of the test shows a very slow heart, around 50 per minute. This and the fall of diastolic pressure explain the unconsciousness that occurred. The clinical sheet classifies D. W. O. in a group well known to the Medical Research Laboratory as the non-compensating type. These men endure the test to a certain limit without any apparent compensation, then, without premonition or warning they collapse completely, usually at a comparatively high oxygen level, though not universally so. The electrocardiogram gives new light on what occurs in the heart of this type at the critical moment of collapse.

Sgt. D. W. O. began the test with the high heart rate of 94 per minute and increased only to 108 during the twenty-five minutes. The usual falling off in the time of the R-T interval occurs, from 0.320 to 0.280 second. There



was also the usual decrease in the T wave. The contractions of the auricle were strong, an amplitude of from 2 to 2.6 mm. for the P wave which continued to 8.6 per cent. oxygen. The T wave was lower and broader in type than the average. As the oxygen want progressed, a sharp negative wave appeared at the terminal portion of the T.

Sgt. D. W. O. became unconscious at the crisis of the experiment, though he retained reflex control of his muscles and sat erect as if asleep. Only a

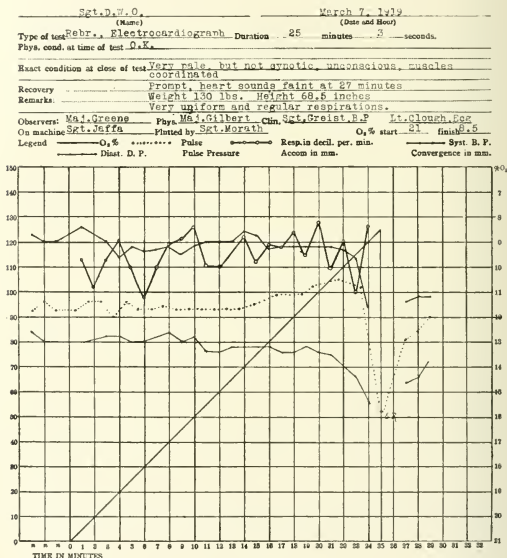


Figure 7

short tracing of seven ventricular contractions was obtained at this critical moment (Plate 6, Fig. 10), 8.5 per cent. oxygen. Reference to the electrocardiogram shows complete obliteration of the P wave and a strong well developed R-T and a weak T of the ventricular complex. Except for the strong R the electrocardiogram was as nearly iso-electric as in any experiment of the entire series. Plate 6, Figure 10 was made during the unconscious stage. The heart rate had dropped to 57 per minute and undoubtedly the circulation was very inadequate.

Recovery occurred promptly, as shown in Figure 11, Plate 6. There was a return of the P with normal amplitude and normal length of the P-R interval. The T slowly recovered its initial amplitude. The rate remained slower than at the beginning of the experiment but recuperated from the depressed rate at the close of the test.

TABLE 11.—SGT. D. W. O., MARCH 7, 1919

Time of run 25 minutes, 3 seconds. Final oxygen, 8.5 per cent.

Trace and Pulse No.	Time	Oxygen, per Cent.	Duration in Seconds			Amplitude in Mm.				
			R-R	P-R	R-T	P	Q	R	S	T
1-6	Normal	21.0	0.640	0.140	0.320	2.2	1.0	20.0	4.0	1.5
2-1	5 min.	18.5	0.660	0.144	0.412	2.6	1.5	18.0	4.5	1.2
3-8	10 min.	16.0	0.656	0.148	0.320	2.6	1.3	18.0	4.4	1.2
4-4	15 min.	13.5	0.632	0.148	0.312	2.2	1.2	17.5	4.0	0.8
5	17 min.	12.6	0.612	0.152	0.320	2.0	1.3	16.0	4.0	0.4
6	19 min.	11.6	0.608	0.160	0.304	2.0	1.4	16.0	3.8	0.3
7	21 min.	10.6	0.592	0.148	0.260	1.5	1.5	18.5	4.0	±0.2
8	23 min.	9.6	0.580	0.140	0.280	2.0	1.8	19.0	4.0	-0.5
9	25 min.	8.6	0.564	0.140	0.280	2.0	2.0	20.0	3.4	-0.8
10-1	25 min.	8.5	1.052	none	0.240	none	1.0	17.0	2.5	0.4
10-2			1.040	none	0.280	none	1.0	19.0	2.6	0.5
10-3			1.080	none	0.240	none	1.0	18.0	2.6	0.2
10-4			1.108	none	?	none	0.8	17.0	?	none
10-5			1.132	none	0.240	none	1.5	20.0	3.0	?
10-6			1.140	none	0.260	none	0.5	18.0	2.5	0.3
11-2	Recovery	21.0	0.868	0.140	0.340	1.4	1.2	19.4	3.2	0.6

TABLE 12.—SUMMARY OF CASES WITH ELECTROCARDIOGRAMS DURING THE LOW OXYGEN TEST

Name	Time Min. Sec.	Terminal Oxygen, per Cent.	Weight, Pounds	Height, Inches	Clinical Remarks
Pvt. N. W. A. ....	21 40	9.7	—	—	
Pfc. H. J. C. ....	22 30	10.0	124	62	Pale, no irregularities of the heart
Cpl. H. B. D. ....	27 20	6.7	145	69	Clonic muscular spasms, pale after 5 minutes
Cpl. F. J. D. ....	24 26	8.1	150	70	Cyanotic, not unconscious
Sgt. M. D. F. ....	33 13	7.3	132	70	
Pvt. J. F. ....	21 56	8.4	132	68	Very cyanotic, spoke in 15 seconds; N. C. A. case
Pfc. A. H. G. ....	29 32	8.1	124	68	
Pfc. T. H. K. ....	27 9	7.1	160	64	Called off at beginning of muscular tremors; clonus severe for 20 seconds; prompt recovery after deep inspiration
Sgt. H. K. ....	30 27	6.5	140	67	Expert diver
Cpl. W. D. L. ....	29 13	6.9	143	69	Clinical history of premature ventriculars, none during test; conscious to end
Sgt. W. C. M. ....	23 48	5.9	212	73	Momentary unconsciousness at end
Sgt. T. B. M. ....	25 54	7.6	134	67	Unconscious, muscles of neck relaxed, recovered in 26 seconds, talked in 56 seconds, pale drowsy and perspiring 5 minutes later
Sgt. E. O. McC. ....	23 5	8.3	166	71	
Pfc. A. H. McD. ....	24 15	7.5	138	65	
Sgt. D. W. O. ....	25 3	8.5	130	68	Unconscious at end, but retained reflex control of muscles, prompt recovery
Sgt. N. S. P. ....	34 12	6.7	138	70	
Sgt. F. J. P. ....	28 2	8.8	130	68	
Sgt. W. A. R. ....	22 50	10.5	146	62	Dazed if not unconscious at end, pale after 3 minutes
Sgt. B. S. ....	24	10.8	135	68	Extreme arrhythmia
Cpl. L. D. S. ....	30 20	1.09	—	—	
Pvt. W. V. T. ....	24 9	8.1	135	69	

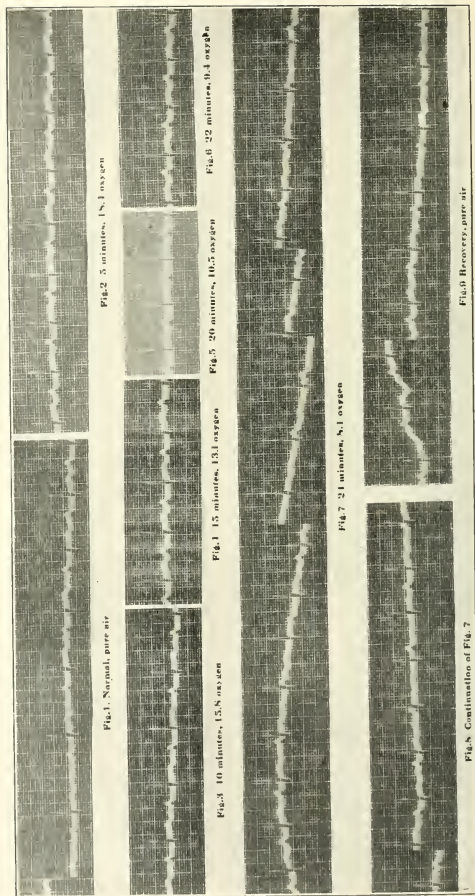


Plate 1. Cpl. F. J. D.

CHANGES IN THE TYPE OF THE ELECTROCARDIOGRAM WITH  
THE ONSET OF OXYGEN WANT

*Comparison of Cases.*—The effects of extreme low oxygen in the air breathed expressed in the electrocardiograms of our twenty-one men are varied and extreme. The degree of oxygen want endured by the majority, thirteen cases, without visible deleterious effects on the heart, is surprising. At least ten of the men reached 10 per cent. oxygen and less with no drastic changes in the electrocardiograms. Of these, five ran to 8 per cent. oxygen and two to less than 7 per cent. The series illustrates the fact established by the general experience of the Medical Research Laboratory that the limit of endurance to low oxygen covers the rather extreme range of from 6 per cent. or less to 10 per cent. and more among vigorous and well developed apparently normal individuals. The men in the series reported now were tested to as low as 5.9 per cent., and taken off at as high as 10.9 per cent.

Seven of the twenty-one men show disturbances of normal heart function, varying from slight and evanescent changes to the most profound and vital interference with normal rhythm and conduction. The extreme changes occurred at the crises of low oxygen, H. B. D., 6.7 per cent.; F. J. D., 8.1 per cent.; J. F., 8.4 per cent.; T. H. K., 7.1 per cent.; W. C. M., 5.9 per cent.; T. B. M., 7.6 per cent.; and D. W. O., 8.5 per cent. Two of the seven had severe clonic muscular spasms which tended to mask symptoms which are the usual signs of impending loss of consciousness. The one clear case in which unconsciousness was not reached out of the seven showing heart irregularities, was that of F. J. D. at 8.1 per cent. oxygen. He developed complete dissociation but with persistence of rather regular auricular and ventricular rhythms. Four of the seven men with extreme heart irregularity were clearly unconscious. In one W. C. M., at 5.9 per cent., the unconscious stage was brief and momentary only, as was also the heart irregularity (Table 3, Plate 10, Fig 8). In the remaining three the cardiac disturbances were more profound, as was also the general evidence of oxygen asphyxiation of the nervous system.

Even casual examination shows that circulatory changes during the rebreather test are slight during the first two thirds of the test. In the last third, the changes come on rapidly until the onset of what we have called the crisis. If the test is pushed still further unconsciousness occurs. Then the disturbances of the heart are rapid, profound, and vital. Twenty seconds at this crisis may suffice to drop the heart rate from its maximum compensating high rate to the profound condition of dissociation observed in F. J. D., or the suppressed auricular beats and slow rhythm of D. W. O. The details are further

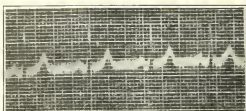
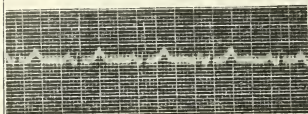
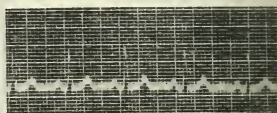
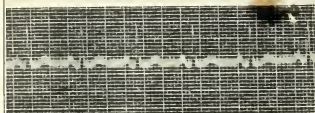
**Fig. 1. Normal, pure air****Fig. 2 5 minutes, 18.1 oxygen****Fig. 3 10 minutes, 15.3 oxygen****Fig. 4 15 minutes, 12.1 oxygen****Fig. 5 20 minutes, 9.5 oxygen****Fig. 6 21 minutes, 8.9 oxygen****Fig. 7 After period, pure air**

Plate 2. Pvt. J. Y.

discussed under two headings, one presenting the general precrisis changes leading up to the crisis or crest of the compensating adjustments, and the other postcrisis and intrinsic changes at and following the crisis.

#### GENERAL OR PRECRISIS CHANGES IN THE TYPE OF THE ELECTROCARDIOGRAM

The primary changes in the general type of the electrocardiogram with the onset of low oxygen are not pronounced and not uniformly constant. A fair proportion (nine cases) show decrease in the time of the conduction, thirteen show corresponding decrease in the time of the ventricular complex with acceleration of rate; two cases show no change, and all show decrease in the amplitude of the T wave. There is no constant association of the change in total time of the conduction and the duration of the ventricular complex in the same individual though association is the rule. The length of the P-R interval is only very slightly influenced by oxygen want up to the crisis, i. e., until the onset of unconsciousness is imminent. There is an appreciable acceleration of the P-R interval at the lower oxygen levels. This amounts in H. J. C. to 6 per cent. acceleration, N. S. F. 12, T. B. M. 7 per cent., etc. These decreases of from 6 to 12 per cent. in conduction time are representative. It is by no means a constant phenomenon. This is not a direct cardiac effect of low oxygen. It is probably bound up in the factors which cause the acceleration in rate. The stimulus that augments the pace making process also hastens conduction.

The R-T interval, or ventricular complex, is also slightly shortened before the crisis is reached. In H. B. D. the normal R-T of 0.320 seconds is reduced to 0.300 and 0.292 seconds in the twentieth minute, 9.5 per cent. oxygen. It is 0.300 seconds in the twenty-seventh minute, 6.8 per cent. oxygen, and promptly returns to 0.320 seconds on breathing pure air. This recovery of the normal time of heart muscle contraction takes place even before the normal S-A rate is re-established in control of the rhythm. The change in contraction time is not profound. It amounts in the case of T. F. K. to a drop of from 0.340 second in the normal to 0.300 second in the twenty-sixth minute at 7.7 per cent. oxygen. This record shows an augmentation in the R-T interval at the fifth minute. However, the low T wave and the occasional uncertainty of its exact termination in Lead II compels us to lay less stress on the slight differences as they appear in tabulation.

In the case of H. K. the electrocardiogram is clear cut and the measurements are more accurate. The table shows a very regular shortening in the R-T with the decrease in oxygen. H. K. was

taken off while still giving normal general reactions. His R-T intervals in the first, fifth and fourteenth contractions of the recovery record are 0.280, 0.300 and 0.320 second, respectively. This is a very prompt and definite return to the original normal. The precrisis decrease in R-T time is coincident with the accelerated rate, and is doubtless due to the same reactive changes. Acceleration in heart rate is primarily at the expense of the quiescent phase of the cycle. This is approximately the iso-electric phase between the T and P waves. Our measurements show that *during the acceleration of rate produced by oxygen want the cardiac processes both of conduction and contraction are hastened*. The acceleration of conduction amounts to from 6 to 12 per cent, and more, and of contraction from 8 to 12 per cent., while the rate is accelerated by from 30 to 70 per cent.

A constant change observed throughout the series is in the character and amplitude of the T wave. The T decreased with low oxygen to the point of complete obliteration in some cases but always by from 50 to 75 per cent. of the amplitude of the normal. The chief change in the T is a simple diminution of amplitude. However, the type form of the complex is also altered. The normal T in Lead II, used by us throughout, is a positive deflection. It is developed slowly and is a symmetrical curve. As extreme oxygen want approaches it becomes much flatter in the positive phase and more abrupt in the negative phase. Or the deflection may be delayed until the very end of the R-T interval. In a few cases the T wave was terminal, slight in amplitude and sharply diphasic, i. e., a short positive followed by an abrupt and short negative, as in the case of D. W. O. (Plate 6, Figs. 8 and 9).

#### CARDIAC CHANGES DURING THE POSTCRISIS OF OXYGEN WANT

The changes in the heart at and following the crisis of oxygen want occur rapidly and are retrogressive in character. The simplest and least complicated change of this type is the development of complete heart block (Cpl. T. J. D). This heart had a history of block. At the time of the test conduction was regular but slow, 0.32 second as against the normal average of from 0.12 to 0.16 second. At 8.1 per cent. oxygen, complete block abruptly developed. The critical period of onset is fortunately recorded in the electrocardiogram, (Plate I, Figs. 7 and 8). Dissociation persisted for the remainder of the test, and, what is of the greatest importance, disappeared promptly on breathing pure air. The weakest link in this heart is the conducting system. The dissociation is definite evidence that *during extreme oxygen want in man the process of conduction in the cardiac conducting system is suppressed*.



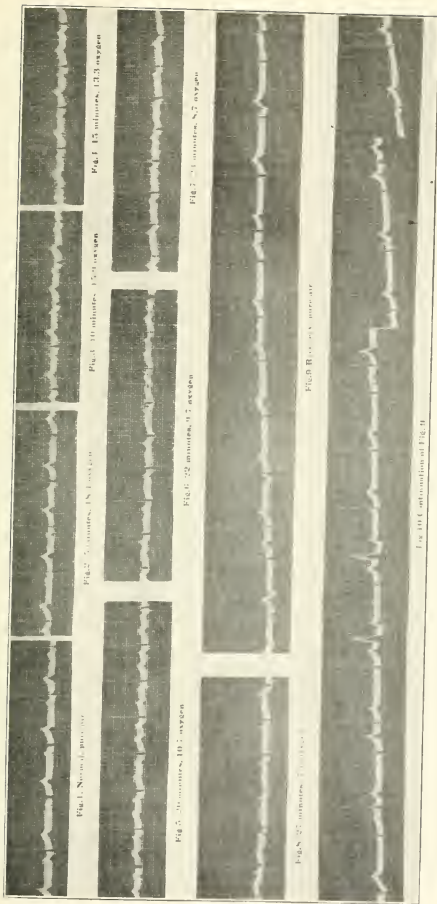


Fig. 10 Continuation of Fig. 9

Plate 3. Pfc. T. H. K.



This test developed the unusual phenomenon of a dissociated heart rhythm in which the auricular rate was slower than the ventricular. The P wave is clearly traceable and well defined, except for two evident buried beats. The ventricular complexes are A-V nodal types. The suppression of conduction in the internodal tissue makes possible the comparison of the two pacemaking centers under identical conditions during oxygen want. The P waves that occur are of the normal erect S-A type during the entire time of dissociation.

The P wave was suppressed in H. B. D. during the twenty-seventh minute, 6.8 per cent. oxygen. The P was absent for the first three beats of his recovery tracing, but the rest of the electrocardiogram shows complete recovery. This is a simple and uncomplicated case of disappearance of the pace-making function of the sino-auricular node with rhythm from the A-V node.

However, the very best illustration of disappearance of auricular rhythm is that of Sgt. T. B. M. At 8.1 per cent oxygen a long series of ventricular complexes occur without a vestige of the P wave. The protocol states the fact that nine ventricular complexes are ideally recorded in which the evidence is clear cut and decisive (Plate 5, Fig. 8).

The momentary partial recovery of an inverted P, and its subsequent loss and second re-establishment, shown in Sgt. T. B. M.'s recovery tracing, gives confirmation of the fact that *there are two fundamental effects that follow oxygen inadequacy, i. e., suppression of rhythm production in the S-A node and block in the internodal conducting tissue. These may occur together or independently.*

An inverted P for a few homogenetic beats followed by its disappearance in T. B. M. is produced wholly by oxygen want. The cardiac complex at this moment is just trembling on the threshold of functional capability, a little less oxygen and it fails completely to function, a little more and it functions normally. It is exactly the phenomenon observed in Sgt. W. C. M. at the corresponding stage. In the latter only the stage of an inverted P and a foreshortened P-R was reached. In the former the record catches the shift in the point of origin of the beat just at the extreme displacement reached by Sgt. W. C. M. and carries the change to the degree of complete suppression of function of all rhythmic tissue above the A-V node. In both instances the complete cycle from the initial state through that of depressed functional activity back to the original was photographed in the electrocardiograms and is presented in the corresponding figures. The actual measurements are given in Tables 9 and 10.

The displacement of the locus of rhythm production is shown in the shortening P-R intervals before the disappearance of the P wave, and by the corresponding increase in the P-R interval during the recovery stages of Sgt. T. B. M.

The complete suppression of function of the sino-auricular node is shown in Plate 6, Fig. 10, at the stage of 8.5 per cent. oxygen in the test of Sgt. D. W. O. This electrocardiogram shows as nearly complete suppression of heart function as one feels safe in producing in man. The rate is slow, about 51 compared with a rate of 83 a few moments earlier. The T is low and flat and the P wave cannot be detected.

The mechanism of the progressive acceleration of the heart during the precrisis period, has not been demonstrated. Evidence appears in our experiments showing that the inhibitory effects through vagus action are slightly increased between the five and fifteen minute stages but are reduced later. This last deduction is justified by the progressive decrease in sinus arrhythmia during the stage of marked acceleration. If the vagus center is responsible for the slow heart rate in the postcrisis stage it must become suddenly and excessively active just when the respiratory center ceases to function. The recovery of sequence contractions with the P wave of normal type but of reduced amplitude, and the P-R interval of normal duration promptly takes place in the after period. The facts seem clear that in man *the slowed rate and suppressed P wave are indicative of suppression of the pace making function of the sino-auricular node and the assumption of that function by the auriculo-ventricular node.* Whether this is due to direct oxygen want on the cardiac tissue itself in man, or is an indirect effect leading to vagospasm in the postcrisis period we cannot at present say. The human observations are not determinative though animal experimentation since the time of Klug indicates that vagospasm is the immediate cause of heart slowing at the crisis of systemic asphyxiation in the presence of carbon dioxid excess.

The terminal electrocardiograms of T. W. K. are of a very much more complicated type. The initial record is normal in type. Only the usual changes in conduction, amplitude and form of the T wave occur through to the 7.7 per cent. oxygen stage, i. e., almost to the end at 7.1 per cent. oxygen. In the tracing during the after period, started apparently before recovery occurred, there is profound upset in the reactions of the intrinsic cardiac mechanism. Heart block is clearly shown. The P wave is present in portions of the record but irregularly spaced and often inverted. The auricular rate, as in F. J. D., is slower than the ventricular rate. There is no P wave in relation to many of the ventricular complexes. If buried in the complex it cannot be shown. Two contractions of muscular origin complicate the irregularity. These facts are easily understood on the theory of suppression of function of the conducting tissue and retention of independent rhythm production in the sino-auricular node or its

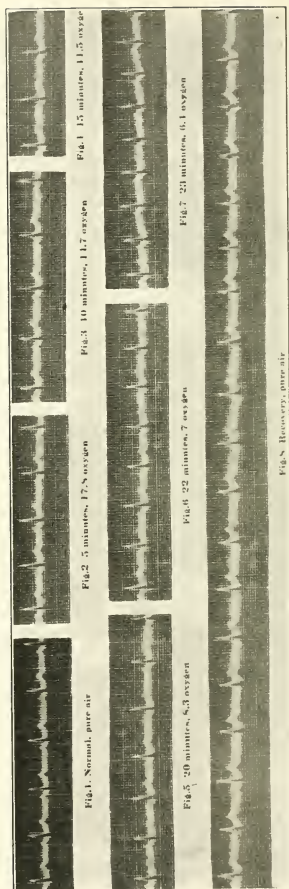


Plate 4. Sgt. W. C. M.

vicinity, coincident with the erect P waves, but auriculoventricular or at least atrial dominant rhythm during the inverted P waves.

#### DISCUSSION OF THE LITERATURE

We do not find any references in the literature dealing with the electrocardiographic method applied to the normal human during anoxemia. The nearest approach to the subject is in the very few cases photographed during the agonal stages of death in which the great excess of carbon dioxide is obvious.

The latest of this type is the study by Halsey<sup>14</sup> of a case of bronchopneumonia. Halsey secured a series of electrocardiograms through to the termination in ventricular fibrillation. His Figure 4 is more or less typical of a heart embarrassed but still beating with a normal sequential rhythm. The halving of the rate and of conduction time, that is "double the time in the earlier record," has never occurred in our tests. Whatever happens to the rate there has never been a multiple lengthening of the conducting time of this type. The unexpected phenomenon shown in Halsey's case is the great slowing of conduction with at the same time maintenance of a strong P wave. The phenomenon is not typical of anoxemia. In our experiments the carbon dioxide was removed but it is certainly present in excess in the dying heart in pneumonia. The gap between Halsey's Figures 5 and 6 is unfortunate, since it is evident that the P waves ceased during the time of that gap in which he has lost the record of the most crucial transitional change in function. The single P in the fourth beat of Figure 6 suggests that Halsey is dealing in this figure with suppression of the S-A nodal rhythm, i. e. by asphyxiation with or without complications.

Robinson<sup>15</sup> made electrocardiographic studies of the mode of death of the human heart. Four out of seven cases showed ventricular activity from 1.5 to 18 minutes after evidence of auricular activity had ceased. Two auricles outlasted the ventricles. In one case the auricle and ventricle stopped together. In three cases complete dissociation occurred. In five cases there was some delay in the conduction. In two cases the auricles ceased before there was any evidence of impaired conduction. There was always a marked slowing during independent ventricular rhythm, the ventricle contracting from fourteen to forty-seven times per minute. There was no auricular but one ventricular fibrillation. He observed interference with both rhythm and conduction, though his published records do not show the onset of the changes in the symptoms. The slowing of the ventricular rates observed by Robinson are confirmed by the slowing obtained by us

14. Halsey: *Heart* **6**:67, 1915.

15. Robinson: *J. Exper. M.* **16**:291, 1912.

when the evidence of auricular contraction disappears. Our rates are at a higher level, but we have not carried the degree of oxygen want to the extreme represented by a heart in the agonal stage during death from infectious disease.

Eyster and Meek<sup>16</sup> produced displacement of the pacemaking function from the S-A node to the A-V node by cooling, by anatomic isolation, by crushing, and by applying chemicals to the S-A node. Their evidence was that rhythm under these conditions never arises outside the parts of the heart containing specialized tissue. The origin of the rhythm is driven down to the atrial node or the A-V node.

Lewis and co-workers in investigations on the lower mammals have shown that both the S-A rhythm and the conduction can be delayed and even suppressed. Lewis<sup>17</sup> also used local cooling to study the development of the displaced beat. Cooling of the S-A node is followed by slowing of the rhythm. His electrocardiograms show that the new center of rhythm production is in the A-V node. Cooling may also interfere with nerve conduction.

Meakins<sup>18</sup> says that "the new rhythm has its origin some distance above the division of the main stem of the auriculo-ventricular bundle." He was able to produce ventricular forward block in the dog by compressing the bundle with a specially devised heart clamp applied after the establishment of A-V rhythm by cooling.

Lewis and Cotton<sup>19</sup> determined an almost constant acceleration of conduction in man as an immediate effect of exercise sufficiently strenuous to produce a considerable acceleration of the heart rate and labored breathing. Such acceleration of conduction does not occur when the acceleration of rate is induced by direct stimulation of the auricles by the application of induction shocks, a fact previously shown by Lewis and Oppenheimer.<sup>20</sup>

Acceleration of conduction would seem to be a function of the reactions of the accelerator nerve induced by the stimulus of exercise, or in our tests by the conditions of reduced oxygen. Lewis and Cotton's conduction time was accelerated by from 0.01 to 0.03 second. Their normal conductions were re-established in from three to five minutes and before the normal rates were re-established. Similar changes in conduction time have been observed in patients from exercise. Our highest acceleration in conduction was 0.048 second. The accelerations in rate which we observed all occurred in the precrisis period, and it was during this time that conduction was quickened.

16. Eyster and Meek: *Heart* **5**: 119, 227, 1914.

17. Lewis: *Heart* **5**: 247, 1914.

18. Meakins: *Heart* **5**: 281, 1914.

19. Lewis and Cotton: *J. Physiol.* **46**: 60, 1913.

20. Lewis and Oppenheimer: *Quart. J. M.* **4**: 145, 1910.

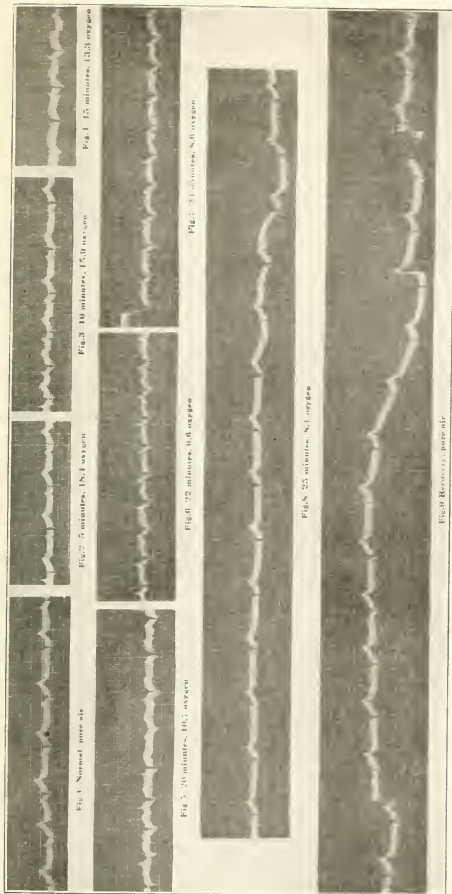


Plate 5. Sgt. T. B. M.

The shorter P-R intervals observed by us at or after the crisis are associated with and explained by the displaced locus of rhythm production and are not accelerated conduction but shortening of the path.

Cohn<sup>21</sup> restudied the physiology of the cardiac vagus pathways showing that the right and left vagi, in dogs at least, do not exercise the same influence on the heart. The right vagus usually exerts a greater control over stimulus production while the left has a profound effect on conduction. Rothberger and Winterberg<sup>22</sup> had suggested earlier that the right vagus and cardiac accelerator nerves are distributed mainly to the S-A node and the left to the A-V node. Cohn and Lewis<sup>23</sup> examined the influence of the vagi in delaying conduction and in producing heart block. They showed that the left vagus usually had the greater effect on conduction, but that the difference was quantitative rather than qualitative. Lewis<sup>24</sup> showed that when the A-V rhythm controls the beat the vagus then acts at the A-V node and its vicinity to produce reversed block. The point is used by Lewis to support the inference that the vagus acts differentially on the conducting tissue above the A-V node. He also observed that in complete heart block in the cat the auricular rhythm of S-A origin completely drops out on deep asphyxiation, a point strictly comparable to our extreme cases of T. B. M. and D. W. O.

Eyster and Meek<sup>24</sup> present electrocardiograms of the disordered action of the heart produced by morphin. Auricular systoles are slowed and even suppressed, or the conduction is partially or completely blocked. Cohn<sup>25</sup> found that after the administration of morphin conduction was blocked and sometimes reversed, as shown by R-P intervals. He asserts that inhibition is the primary picture of morphin action if the right vagus only is intact, while disturbances of conduction predominate with intact left vagus. Cohn states that there is complete parallelism between morphin disturbances and right or left vagal stimulation, and that the heart is released from morphin by atropin or by freezing the vagus. Wilson<sup>26</sup> has shown that the A-V rhythm can be induced readily by vagus stimulation during the early stages of the action of atropin in young people, from eight to fifteen minutes. The A-V rhythm appeared spontaneously in three cases. A-V rhythm could not be induced in his normal cases before atropin was given, or after its maximal effects appeared. It was observed in two cases

21. Cohn: J. Exper. M. **16**:732, 1912.

22. Rothberger and Winterberg: Arch. f. d. ges. Physiol. **135**:559, 1910; **141**:343, 1911.

23. Cohn and Lewis: J. Exper. M. **18**:739, 1913.

24. Eyster and Meek: Heart **4**:59, 1912.

25. Cohn: J. Exper. M. **18**:715, 1913.

26. Wilson: Arch. Int. Med. **16**:989 (Dec.) 1915.

of cardiac disease. These records are of peculiar value and interest in that figures are given of simultaneous venograms that show coincidence of As and Vs waves with electrocardiograms under the initial atropin vagus stimulation. The electrocardiograms alone give no evidence of the P wave (Wilson's Fig. 4, A-V rhythm of Type 2).

Robinson and Auer<sup>27</sup> state in their papers on anaphylactic shock that marked changes occurred in heart activity in twenty-two out of twenty-four anaphylactic rabbits, whether the vagi were cut or not. In the dog "These cardiac changes consist of disturbances in conduction of the heart impulses, abnormalities in the ventricular contractions, and other unusual disturbances of the mechanism of the heart beat." They find inversion of the P wave, shortening of the P-R interval showing displacement of the pacemaker, and varying degrees of dissociation. The relationship between auricular and ventricular activity becomes disturbed "as shown by the abnormal proximity of the P and R waves (Fig. 15)." Their figure shows a P-R of 0.033 as against the pre-experimental time of 0.08 second. They say "it probably represents a change at the point at which the stimulus of the heart arises." This general picture coincides very well with the observed changes in our charts for T. B. M., D. W. O., and J. D., also for W. C. M. Robinson and Auer interpret the changes in the form of the ventricular complex in anaphylaxis as peripheral and local. The anaphylactic results are equally well explained on the hypothesis of vagal stimulation.

Lewis, White and Meakins<sup>28</sup> studied the effects of asphyxiation on conduction in the heart of the cat by the method of first cooling the S-A node and then allowing asphyxiation to develop by stopping artificial respiration, also by the method of simple asphyxiation without cooling. These methods make possible the study of asphyxial effects on conduction during the normal S-A rhythm in contrast with the type of rhythm of A-V origin. Their facts are developed by splendidly executed electrocardiograms. The conclusions emphasized by the authors are "(1) Asphyxia produces a gradually increasing *forward* heart block in the cat's heart beating from the S-A node. (2) It produces a gradually increasing *reversed* heart block when the heart chambers respond to the A-V node. (3) The main defect is in the portion of the functional system lying at a higher level (nearer the auricle) than the actual seat of impulse discharge in the A-V rhythm. (4) The A-V node or tissue in its immediate vicinity is the most susceptible tissue in respect of changes in the A-V conduction. (5) In the cat, so asphyxiated that there is a complete functional break between A-V node and auricle, the application of cold to the S-A

27. Robinson and Auer: J. Exper. M. **18**:556, 1913.

28. Lewis, White and Meakins: Heart **5**:289, 1914



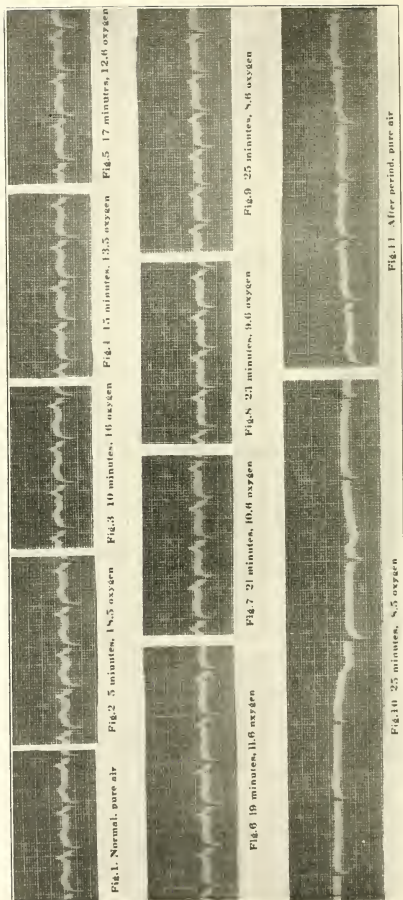


Plate 6. Sgt. W. D. O.

node brings about standstill of the whole of the auricular tissue. (6) The effect of the vagal stimulation in the automatic ventricle, as reported by Van Angyan, are regarded as the effects of vagal stimulation upon the A-V rhythm, for in the complete block of asphyxia the dissociated ventricle is controlled by the A-V node. (7) When at the end of simple asphyxia of the cat the auricular contractions disappear abruptly during the stage of complete A-V dissociation, the change is attributed to depression of the pacemaker, the A-V node continuing to control the movements of the ventricle."

Mathison<sup>29</sup> did not observe heart block on administering an excess of carbon dioxide, but when he produced asphyxia by nitrogen containing only 1 or 2 per cent. oxygen, thus preventing an excess of carbon-dioxide in the tissues, he observed heart block as "a regular occurrence during asphyxia in dogs." Block still occurred when the vagi were cut. He attributes the block to want of oxygen alone on the cardiac tissues.

Most of the investigations in this field have dealt with asphyxia produced in the usual way by cessation of respiratory movements. Both an increase of carbon dioxide and a decrease of oxygen takes place. Mathison has excluded the carbon dioxide factor in mammals. In Lewis' series of experiments the added factor of local cooling of the S-A node occurs, which adds to the complexity of experimental conditions. The rebreather method used by us eliminates the carbon dioxide by absorbing it from the exhaled air. There is, indeed, a reduction of the degree of saturation of carbon dioxide in exhaled air during the stage of augmented respiratory volume. We have recounted in careful detail the changes observed in the normal human heart that follow on simple oxygen want produced by gradual and progressive reduction of the available oxygen in the blood and body tissues to a level below which normal function can no longer occur. We reaffirm that *rhythm production in the human heart is decreased and lost at the S-A node, dissociation and block occur, and both the factor of rhythm and of conduction are lost in the descending direction during extreme oxygen want and in the absence of excess of carbon dioxide.*

These cardiac changes obviously may occur from simple oxygen want directly affecting the tissues of the heart, so that the heart can not maintain its normal function. Or the changes may be due to nerve influence as a result of asphyxial vagospasm, as shown by Mathison<sup>29</sup> to occur in dogs with intact vagi though he stressed the local effects. Much of our data, for example, the case of T. H. K., is not satisfactorily explained by the vagus theory, while cases like those of T. B. M. and D. W. O. look more typical of vagus inhibitions. To explain our

29. Mathison: Heart 2:54, 1910.

terminal heart slowing and the loss of auricular beats on the hypothesis of vagus stimulation is to admit a sudden vagospasm at the close of a long period of increasing heart acceleration associated with evidence of early disappearance of normal vagal activity. Crucial tests on man are not without risk. However, we have assumed as much risk as one dares and will further discuss the significance of these changes in a paper now in preparation giving the results of a second series of electrocardiographic experiments in extreme anoxemia.<sup>30</sup>

#### SUMMARY

1. The general changes in the type of the electrocardiogram of man with progressively induced oxygen deficiency in the air breathed are slight and compensating until a certain critical stage or crisis is reached, then fundamental intrinsic changes in the cardiac mechanism begin.

2. The general and precrisis changes are: (a) There is a decrease or shortening of the time of the P-R interval an acceleration in conduction time, known also to be coincident with augmentation of heart rate from exercise. This augmentation is not universally observed. (b) There is a decrease in the total time of the R-T interval similar in type and reaction frequency to the change in conduction time but not always associated in the same test, and (c) there is a marked decrease in the amplitude of the T wave, with a retardation towards the terminal phase of the moment at which the maximum deflection appears. Sometimes the T wave becomes diphasic or negative at or near the crisis.

3. The precrisis electrocardiographic changes are associated with other compensating reactions to oxygen want, reactions that are expressed in the general increase in heart rate and blood pressure, and in the respiratory augmentation in minute volume of air breathed.

4. The chief postcrisis changes in the heart from extreme oxygen want are: (a) a great slowing of rate, (b), progressive descending displacement of the pacemaker or center of rhythm production toward and into the A-V node, and (c) interference with normal conduction leading to dissociation.

5. The postcrisis heart rate rapidly drops to a slow rhythm, in a minute or less, often in a few seconds. It decreases from 120 or 130 to 50 or 60 per minute, a drop of 50 per cent, and more. This change is associated with the development of a rhythm of auriculoventricular origin, six cases. The sino-auricular rhythm was slowed coincidentally

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30. Greene and Gilbert: Proc. Am. Physiol. Soc., Am. J. Physiol. **51**:181, 1920. This reference presents a preliminary report in brief abstract of the findings given in the present paper.

and disappeared altogether in extreme tests, three cases. Recovery of S-A rhythm was prompt on breathing atmospheric air.

6. In the posterisis stage conduction was suppressed leading to complete dissociation with maintenance of auricular beats, two cases. Complete suppression of conduction occurred or was suspected in cases of absence of the *P* wave, three cases.

7. Suppression of cardiac function during oxygen want occurred in the descending direction and recovery in the reverse direction, both as regards rhythm production and conduction.

8. Experimental tests have never been carried to the point of complete suppression of the rhythm of the A-V node, or of the conducting system connecting that node with the musculature of the ventricles in man.

9. Discussion is offered comparing the hypothesis of asphyxial vagospasm and that of direct oxygen want in the tissue as mechanisms responsible for the phenomena observed in the human heart, but deciding evidence is not yet available.\*

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\* We are under particular obligation to the commanding officers of the Medical Research Laboratory and of the U. S. General Hospital No. 9. We are also under personal obligation to Lieut. Harry Clough, who had charge of the hospital cardiographic station and under whose skill the excellent electrocardiograms were made. To the men who took the tests to the extreme limits of safety, and to the noncommissioned officers who assisted in the examinations we express appreciation and acknowledgments.

## THE DETERMINATION AND SIGNIFICANCE OF THE ELECTRICAL AXIS OF THE HUMAN HEART\*

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The subject of the electrical axis of the heart has been receiving more and more attention in recent years. In the first edition of Lewis' work "The Mechanism of the Heart Beat"<sup>1</sup> it is not mentioned. Considerable attention, however, is given the subject in the second edition.<sup>2</sup> It is not too much to say that a thorough understanding of the relations of the axis is a necessary foundation of knowledge of apparently simple features of the electrocardiogram. This paper has for its purpose the presentation of a new method of evaluating the electrical axis, and a brief discussion of some aspects of the study of the subject.

### DEFINITION

By the term "electrical axis" is meant the line along which the resultant of the electrical forces acting in the heart at any instant is expressed. Or, from another point of view, it corresponds, as Lewis puts it,<sup>2</sup> to "the average direction in which the excitation wave is tending to move at the corresponding instant of time." This axis then is constantly shifting during the progress of the excitatory process. Therefore, one speaks of "the" electrical axis only in a more restricted sense, meaning an axis at a particular instant or a resultant axis.

### TERMINOLOGY

The electrical axis was first discussed by Waller,<sup>3</sup> and this worker has subsequently made many observations in this field. Waller arrived at the idea of the electrical axis by seeking an explanation of the different values of corresponding deflections of the galvanometer string obtained in various leads. His system of leads is relatively complicated and his terminology is obscure. The direction of the electrical axis is

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1. Lewis, T.: *The Mechanism of the Heart Beat*, London, 1911.

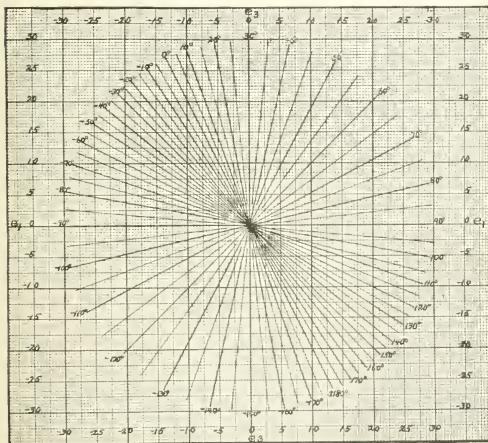
2. Lewis, T.: *The Mechanism and Graphic Registration of the Heart Beat*, London and New York, 1920.

3. Waller, A. D.: *Electromotive Properties of the Human Heart*, Brit. M. J. 2:751 (Oct. 6) 1888. *Electromotive Changes Connected with the Beat of the Mammalian Heart*, Phil. Tr. Roy. Soc. London, B 80:169, 1889.

expressed in terms of trigonometry. Waller worked out empirically, and later <sup>4</sup> proved geometrically a rather simple formula for the calculation of the angle between the electrical and the vertical axes:

$$(1) \tan a = 2 \frac{R - L}{R + L}$$

in which "a" is the angle between the electrical and the vertical axis; R is the value of the deflection derived from the right arm and left foot, and L is the value of that derived from the left arm and left foot. This formula can, of course, be used for Einthoven's angle "a" des-



Angle "a" in terms of  $e I$  and  $e III$ . For description see text.

cribed below by substituting "cotangent a" for "tangent a." Waller's usage has not been followed by writers on the subject.

Our terminology is that of Einthoven.<sup>5</sup> Selecting from the number of leads available the three in common use, he showed that the values-

4. Waller, A. D.: Various Inclinations of Electrical Axis, Pt. I, Proc. Roy. Soc. London, B **86**:507 (July) 1913.

5. Einthoven, W.: Le Télécardiogramme, Arch. Internat. Physiol. **4**:132, 1906. Weiteres über das Elektrokardiogramm, Arch. f. d. ges. Physiol. **122**: 517 (May) 1908.

of the deflections so obtained are related as in his equation, according to which at a given instant in the cycle of the heart beat, the value of Lead II is equal to the sum of the values of Leads I and III.

$$(2) \text{ Lead II} = \text{Lead I} + \text{Lead III}$$

He later explains this relation by comparison with the movement of a force within an equilateral triangle in which the projections of the course of the force on the sides of the triangle necessarily obey this law. The proof of this is conveniently presented in Mann's recent paper.<sup>6</sup> A line between the center of the triangle and any point on the course of the moving force would represent the electrical axis at that instant. The values of the deflections, and, hence, of the length of the axis are expressed in tenths of a millivolt. Einthoven refers to the length of the axis as the "manifest" value, but the term "absolute" would be clearer. The axis is defined by the angle, called "*a*," between its plane and the horizontal, which is taken as the zero line. Angles above the horizontal are referred to as negative while those below are said to be positive. This is contrary to our mathematical usage, as pointed out by Carter,<sup>7</sup> but it would seem best in view of the extensive work of Einthoven,<sup>8</sup> Lewis,<sup>9</sup> and Fahr<sup>10</sup> to continue to use this terminology.

#### FINDING THE ANGLE

The fundamental equations showing the relations of the leads and the length and direction of the axis as worked out by Einthoven, Fahr and de Waart<sup>8</sup> are:

$$(3) e_1 = E \cos a$$

$$(4) e_2 = E \cos (a - 60^\circ)$$

$$(5) e_3 = E \cos (120^\circ - a)$$

In which  $e_1$ ,  $e_2$  and  $e_3$  represent the values of the deflections in the three leads respectively;  $E$  is the manifest value or length of the axis and "*a*"

6. Mann, H.: Method of Analyzing the Electrocardiogram, *Arch. Int. Med.* **25**:283 (March) 1920.

7. Carter, E. P.; Richter, C. P., and Greene, C. H.: Graphic Application of the Principle of the Equilateral Triangle, etc., *Johns Hopkins Hosp. Bull.* **30**:162 (June) 1919.

8. Einthoven, W.; Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grosse, etc., *Arch. f. d. ges. Physiol.* **150**:275 (March) 1913.

9. Lewis, T.: Spread of the Excitatory Process, *Phil. Tr. Roy. Soc. Lond.* **207**: B, 221, 1916.

10. Fahr, G. E.: Analysis of Spread of Excitation Wave, *Arch. Int. Med.* **25**:146 (Feb.) 1920. Fahr, G., and Weber, A.: Ueber die Ortsbestimmung der Erregung im menschlichen Herzen, *Deutsch. Arch. f. klin. Med.* **117**:361 (June) 1915.

the angle between the axis and the horizontal. From these data formulas were evolved the determination of "a" as follows:

$$(6) \tan a = \frac{2 e_2 - e_1}{e_1 \sqrt{3}}$$

$$(7) \tan a = \frac{2 e_3 + e_1}{e_1 \sqrt{3}}$$

$$(8) \tan a = \frac{e_1 + e_3}{(e_2 - e_3) \sqrt{3}}$$

On the basis of these formulas, Einthoven published tables by which the angle "a" may be determined after the values of the deflections are reduced proportionately so that the greatest is equal to 10. In a later article<sup>11</sup> is another table based on the same principle differently applied. One or the other of these tables, chiefly the former, has been used in the past by most of those interested in this subject.

Pardee<sup>12</sup> has shown that it is possible to tell by inspection of the positivity or negativity of the three leads in which quadrant the axis lies. This is because no combination of signs in the three leads occurs in more than one quadrant, which is a direct consequence of the geometric relationship pointed out by Einthoven.<sup>8</sup>

Fahr and Weber<sup>10</sup> proposed a method of direct geometric construction of the angle. The values of the deflections in two leads are measured off in any units convenient on lines inclined to one another at an angle of 60 degrees. The line representing the electrical axis runs from the vertex of the angle of 60 degrees through the junction of perpendiculars erected at the points measured off. This method is cumbersome and does not lend itself to routine use, especially in the case of angles less than 0 or greater than 90 degrees.

Recently from this laboratory Carter, Richter and Greene,<sup>7</sup> independently of the previous suggestion, set forth an adaptation of the same principle to the equilateral triangle. In this method a figure is used in which the geometric construction of the lead values commonly met is inserted in an equilateral triangle, about which is circumscribed a concentric circle appropriately divided into degrees. Thus the angle is found by the projection on the circle of a straight line through the center and through the point representing the lead values. This method has been in constant and extensive use in this laboratory since its inception.

In the new edition of the "Mechanism" Lewis<sup>2</sup> offers for use a figure showing the relative values in the three leads of a given manifest

11. Einthoven, W.; Bergansius, F. L., and Bijtel, J.: Gleichzeitige Registrierung elektrischer Erscheinungen, etc., Arch. f. d. ges. Physiol. **164**:167 (June) 1916.

12. Pardee, H. E. B.: Form of the Electrocardiogram, J. A. M. A. **62**:1311 (April 25) 1914.



value, and the changes they undergo as the axis rotates from 0 through 180 degrees to 0 again. This is not of practical value because of the difficulty, amounting almost to impossibility, of proportioning the lead values of widely varying manifest values at unknown angles.

In an interesting variation of the geometric method, Mann plots the manifest values at successive moments and connects the points by a smooth curve.<sup>6</sup> He uses rectangular co-ordinates of which "x" is given directly by the value of Lead I and "y" must be calculated by a formula from the values of Leads II and III. The result is a "monocardiogram" which is essentially the figure obtained by connecting the ends of the electrical axes as charted by Williams.<sup>13</sup> It may be plotted directly on the equilateral triangle divided as in Carter's Figure 5, without the necessity of calculating the "y" value.

It should be noted that Mann in his figures reverses the direction of the deflections in all the leads as related to the triangle, and plots positive values of "x" (=Lead I) to the left. This is at variance with the standard method of connecting the lead derivations with the string. That is, in taking the leads the lower end of the string is connected with the derivation which is normally negative, or corresponds to the zinc pole of a Daniell cell. In normal cases, therefore, the current travels down the string which is thereby deflected to the observers's right (provided the polarity of the electromagnet be properly adjusted), the movement being later described as upright. Compare Mann's Figure 2 with Lewis' Figure 13 and Williams' Figure 5.

#### THE METHOD SUGGESTED

As Einthoven pointed out, there is a constant ratio between the values of the three leads with a given electrical axis.<sup>8</sup> It also follows from his formulas, 6, 7 and 8 above, that the angle "a" is determined by the ratio between the values of any two leads. This is readily apparent on inspection of the triangle as presented by Carter. But none of the methods suggested for evaluating the angle "a" has taken advantage of this relation, although it is, indeed, the most simple and fundamental relationship between the lead values and the angle "a." Table 1 gives the ratios between the values of Leads I and III at the various angles. Such a table is very much more simple to use than those of Einthoven. The ratios are derived by dividing equation (3) by equation (5), thus:

$$(9) \quad \frac{e_1}{e_3} = \frac{E \cos a}{E \cos (120 - a)}$$

$$(10) \quad \frac{\cos a}{\cos (120 - a)} = \frac{e_1}{e_3} = \text{ratio desired.}$$

13. Williams, H. B.: Cause of Phase Difference, etc., *Am. J. Physiol.* **35**: 292 (Oct.) 1914.

Table I is presented graphically in Figure 1, a chart which has been found very easy to use and which gives the result quickly. The ordinates represent values of Lead I, positive above and negative below the horizontal axis. The abscissae represent values of Lead III, positive to the right and negative to the left of the vertical axis. The values of the angles "a" are represented in accordance with Table 1, at the intersections of the lead values giving the proper ratios. To take an example, suppose the values + 9.5 and + 16.5 are accepted for Leads I and III of an electrocardiogram. In using the chart, one locates the point representing these values and the angle "a" is given by the relation of that point to the radii drawn in. In this case, the point representing  $e_1 = + 9.5$  and  $e_3 = + 16.5$  is approximately at - 69 degrees. Also the ratio in this case is 0.57 + which the table of ratios shows to correspond to between + 70 degrees and + 65 degrees, much nearer the former. This figure gives the value of the angle "a" with all the accuracy that is desirable.

TABLE 1.—THE ANGLE "a" IN TERMS OF THE RATIO,  $e_1/e_3$ . TO FIND THE ANGLE "a" DIVIDE THE VALUE OF LEAD I BY THAT OF LEAD III AND UNDER THE PROPER SIGNS FOR THE LEADS SEEK THE ANGLE OPPOSITE THE RATIO SO OBTAINED

Ratio	Angle "a"		Ratio	Angle "a"		Ratio	Angle "a"	
	$e_1 + / e_3 +$	$e_1 - / e_3 -$		$e_1 + / e_3 -$	$e_1 - / e_3 -$		$e_1 + / e_3 -$	$e_1 - / e_3 -$
0.0	+ 90°	- 90°	0.0	- 90°	- 90°	- 1.11	- 25	+ 155°
+ 0.11	85	- 95	- 0.10	- 85	95	- 1.23	- 20	140
0.23	80	- 100	- 0.19	- 80	100	- 1.37	- 15	165
0.37	75	- 105	- 0.27	- 75	105	- 1.53	- 10	170
0.53	70	- 110	- 0.35	- 70	110	- 1.74	- 5	175
0.74	65	- 115	- 0.42	- 65	115	- 2.00	0	+ 180
1.00	60	- 120	- 0.50	- 60	120	- 2.36	+ 5	- 175
1.36	55	- 125	- 0.58	- 55	125	- 2.88	10	- 170
1.88	50	- 130	- 0.65	- 50	130	- 3.73	15	- 165
2.73	45	- 135	- 0.73	- 45	135	- 5.41	20	- 160
4.41	40	- 140	- 0.82	- 40	140	- 10.40	25	- 155
9.40	35	- 145	- 0.90	- 35	145	- ∞	30	- 150
∞	30	- 150	- 1.00	- 30	150			

The manifest value which is represented by E, is determined by the value of any lead and the angle "a." To use the value of Lead I, for example, one takes equation (4) above:

$$(4) \quad e_1 = E \cos a$$

$$(11) \quad E = \frac{e_1}{\cos a}$$

$$(12) \quad E = e_1 \frac{1}{\cos a}$$

It follows from this last equation (12) that one can determine the manifest value by multiplying the value of Lead I as measured by the reciprocal of the cosine of the angle "a." Table 2 gives the values of  $\frac{1}{\cos a}$  at intervals of five degrees, with interpolation values for one

degree. In the higher values the interpolations lead to slight errors, which are inevitable. (For the angle "a" = +90 degrees we cannot use Lead I as the factor  $\frac{1}{\cos a}$  is infinity; hence Lead III is substituted.) Suppose, for example, Lead I = 5 and "a" = 65 degrees. Then  $\frac{1}{\cos a} = 2.37$ , which multiplied by 5 gives 11.85, the value of E.

TABLE 2.—THE VALUE OF  $\frac{1}{\cos a}$ . THE MANIFEST VALUE IS OBTAINED BY MULTIPLYING THE VALUE OF LEAD I BY THIS FACTOR

Angle "a"		$\frac{1}{\cos a}$	Interpolation for 1°	Angle "a"		$\frac{1}{\cos a}$	Interpolation for 1°
±0°	±180°	1.000	0.001	±50°	±130°	1.56	0.035
5°	175°	1.004	0.002	55°	125°	1.74	0.05
10°	170°	1.015	0.004	60°	120°	2.00	0.07
15°	165°	1.035	0.006	65°	115°	2.37	0.11
20°	160°	1.064	0.008	70°	110°	2.9	0.2
25°	155°	1.104	0.01	75°	105°	3.9	0.4
30°	150°	1.155	0.013	80°	100°	5.8	0.9
35°	145°	1.221	0.017	85°	95°	11.5	
40°	140°	1.305	0.022	90°*	....	1.155*	0.013*
45°	135°	1.41	0.03				

\* For "a" = 90° use lead III.

It should be emphasized that all these "methods" have the same underlying principle and with the exception of that of Waller as explained above, are designed to reach the same result.

In practice two difficulties arise in connection with the determination of the angle "a." First, since the electrical axis is constantly shifting throughout the cycle of the heart beat, what axis or axes shall be determined? For certain purposes it is helpful and of great interest to determine the direction of the axis at short intervals throughout the cycle or a part of it. Tabulation of the results, showing clearly the mode of shifting present, is very instructive.<sup>14</sup> But for practical reasons this is only possible in a limited number of cases. In general, the axis is determined only for that time instant when the greatest potential difference is recorded by one or more of the leads, i. e., at the peak of the Q R S complex. This is then spoken of as "the" electrical axis; but in many ways this is misleading. It is not unlikely that as the subject is developed it will appear that the axis should be determined at different instants for different purposes.

Secondly, what parts of the curves in the two or three leads shall we measure? The law of the relationship of the leads is only true of corresponding time instants in the leads. It has been shown that the peaks are often not in phase. Strictly, then, simultaneous leads or leads taken with simultaneous phonocardiograms should be used.<sup>15</sup> Unfor-

14. Grau, H.: Ueber der Einfluss der Herzlage auf die Form des Elektrokardiogramms. *Ztschr. f. klin. Med.* **69**:281, 1910.

15. Fahr, G.: Simultaneous Records of Heart Sounds and the Electrocardiogram, *Heart* **4**:147 (Nov.) 1912.

tunately neither of these methods is available for extensive application. Lewis<sup>9</sup> adjusts enlarged graphs of the three leads, one above the other, until the measured values in all leads at a number of instants are all within the law that Lead II is the sum of Leads I and III. This is the most satisfactory method which is at present available. For the routine determination of the electrical axis in a large number of cases we can only use the values of the peaks of the Q R S group. In general this gives a value which is not widely at variance with the accurate value of the angle "*a*" for the time chosen.

#### THE NORMAL ELECTRICAL AXIS

It has been found that the vast majority of normal electrocardiograms show electrical axes at the instant of greatest potential difference that lie within a restricted portion of the compass. Different observers have placed varying limits upon the normal variation but the precise limits are not matters of great importance. Einthoven, Fahr and de Waart<sup>8</sup> placed the normal limits at 40 and 90 degrees, Waller<sup>16</sup> at —10 degrees and 100 degrees. Carter and Greene<sup>17</sup> adopted 0 degrees and 90 degrees which may be followed provided too much emphasis be not placed on slight variations beyond these limits. This limitation certainly embraces nearly all normal cases.

Certain important practical points are explained by consideration of the electrical axis and the manifest value. A few of these may be briefly outlined.

#### THE EFFECT OF RESPIRATION

The angle "*a*," as is now well-known, changes with respiration, being greater in inspiration and less in expiration.<sup>18</sup> In more general terms, the same changes occur respectively with descent and ascent of the diaphragm, whatever the cause (compare, for example, the effect of gastric distention). The change in direction of the axis is from 5 to 35 degrees in extent. The form of the electrocardiogram as a rule, is not altered by this change, though the height of the chief ventricular waves in Leads I and III always varies somewhat with the respiratory phase. Lead II shows the variation more rarely and to a less degree for the reason that most axes are more nearly parallel to the plane of that lead and variations in the angle under that condition have less effect upon the value of the lead. This can be seen expressed mathematically for Lead I in Table 2.

16. Waller, A. D.: Various Inclinations of Electrical Axis, Pt. 1A, Proc. Roy. Soc. Lond., B **88**:49 (Aug.) 1914.

17. Carter, E. P., and Greene, C. H.: Electrocardiogram and Ventricular Preponderance, Arch. Int. Med. **21**:638 (Dec.) 1919.

18. Waller, A. D.: Effect of Respiration on Electrical Axis, J. Physiol. (Proc.) **46**:57 (Aug.) 1913.

It has, however, often been observed<sup>19</sup> that certain electrocardiograms show a change of R to S in Lead III and certain others a change of S to R in the same lead. It is Lead III which shows this change because the various axes are usually more nearly at right angles to the plane of this lead and therefore slight changes of direction have marked effects upon the value of the lead. A glance at Figure 1 shows the geometric explanation of the change in direction of the waves. At the angle 30 degrees Lead III is equal to 0, or, in other words, the current direction is at right angles to the lead plane and no movement of the string is recorded. At angles below 30 degrees Lead III has a negative value and above 30 degrees a positive value. Hence, in a heart whose axis is close to 30 degrees the value of Lead III may be changed from positive to negative by a good expiration; or, vice versa, by a deep inspiration depending on which side of 30 degrees the axis starts from. It should be noted that in most cases these changes are produced only by respiratory movements of more than normal excursion.

The peculiarity of Lead III just discussed underlies the widespread feeling that alterations in this lead should not be emphasized. But it would be better to bear this explanation in mind and use Lead III for whatever information it may contribute. Interestingly enough it will be seen that in cases of "situs inversus" Lead II becomes the unstable lead and Lead III relatively stable.

In measuring curves which show a marked respiratory variation in excursion the high R values in Lead I should be taken in conjunction with low R values or with high S values in Lead III. This follows from the direction in which the axis shifts as explained above.

#### THE EFFECTS OF THE POSITION OF THE BODY

Moderate changes in the position of the body have but little effect on the electrical axis. The angle "a" is from 10 to 15 degrees greater in the standing than in the sitting or in the prone position. It is usually about the same when the patient is lying on his back as it is when he is seated. In the left lateral decubitus the angle "a" is increased by about 15 degrees, and decreased somewhat less in the right lateral decubitus.<sup>19</sup>

#### EFFECT OF OTHER DISPLACEMENTS OF THE HEART

One of the earliest observations<sup>20</sup> in this field was of the effect of "situs inversus." Here the effect is complete and the explanation obvious.

19. Waller, A. D.: Voluntary Reversal of Human Electrocardiogram by Deep Respiration, *J. Physiol. (Proc.)* **48**:40 (July) 1914.

Alterations in the position of the heart produced in other ways, in general, do not have marked effects. Pneumothorax, pleural effusion and similar conditions cause but slight shifting of the electrical axis.

#### VENTRICULAR PREPONDERANCE

In the minds of many the subject of the electrical axis is linked inseparably with that of ventricular predominance because it is in this connection that the axis finds its most obvious clinical application. It was first pointed out by Einthoven<sup>2</sup> that "hypertrophy" of one or the other ventricle is associated with characteristic electrocardiographic findings, now too well known to need repetition. These peculiarities were definitely related to the anatomical conditions by two series of hearts examined by Lewis<sup>20</sup> and Cotton.<sup>21</sup> At the same time, Lewis suggested that in this connection the term "preponderance" rather than "hypertrophy" should be used. It should be recalled that there is normally a left ventricular preponderance present. The normal weight ratio, L/R, probably ranges between 1.6 and 2.1. When the expression left preponderance is used, then, it means that the left ventricle is thought of as weighing more than 2.1 times as much as the right ventricle.

The features of the electrocardiogram under discussion are such that they can only be interpreted as reflections of peculiarities of the electrical axis. The "high R" in Lead I and "deep S" in Lead III signify a negative angle "a" (S in Lead III first appears at an angle of 30 degrees). The "S" in Lead I and "high R" in Lead III are projections of an axis at an angle greater than 90 degrees (S in Lead I first appears at that angle). Lewis and his co-workers<sup>2</sup> have shown that the underlying change in the axis concerns the direction in which it rotates. Normally, the electrical axis rotates uninterruptedly in a clockwise direction. In case of right ventricular preponderance the rotation is in the same direction but very quickly reaches high values for "a" and extends farther. When the left side is preponderant, the direction of rotation is counter-clockwise and the extreme deflections are at negative angles. These departures from the normal are due to a disturbance in the relation between the dextrocardiogram and levo-cardiogram of which the ordinary electrocardiogram is a summation.

So much it would seem is beyond controversy. Lewis<sup>2</sup> says there is little reason to doubt that Einthoven's conclusions are valid, and strongly suggests that it should not be assumed in case of incompatibility between clinical and electrocardiographic evidence that the latter

20. Lewis, T.: Observations on Ventricular Preponderance, etc., *Heart* 5: 367 (July) 1914.

21. Cotton, T.: Observations on Hypertrophy, *Heart* 6:217 (Oct.)-1917.

is necessarily at fault. The suggestion that dilatation rather than mass preponderance may sometimes be present has been made by Waller<sup>22</sup> and by Fahr,<sup>23</sup> a suggestion which in the light of our present knowledge needs supporting evidence. In a recent paper Fahr<sup>24</sup> has advanced the theory that the abnormalities of the electrocardiogram under discussion are due to changes in the relations between the lengths of the bundle branches on the two sides. This theory is at present without a satisfactory experimental basis.

In using the electrical axis for the purpose of estimating ventricular preponderance fixed limits of normality are necessary, and 0 to 90 degrees may be used, provided one bears in mind three points. First, that the normal respiratory variation may be as much as 30 degrees. Secondly, that it is not intended to attach much significance to angles just beyond the limits of normality. And thirdly that there are other causes of abnormal angles, such as "situs inversus" and bundle branch blocks. With regard to the limits defined above, it is easy to remember that the angle "a" is negative when the value of Lead III is negative and the ratio between the value of Lead I and that of Lead III is less than 2 (a negative value in Lead III does not necessarily mean a negative angle). A negative value in Lead I in conjunction with a positive value in Lead III, however, always means an axis at an angle greater than + 90 degrees.

Carter and Greene,<sup>16</sup> in a paper from this laboratory, endeavored to show the general correspondence between the angles of the greatest potential difference developed and the ratios between the weights of the ventricles in the few cases (fifteen in all) in which the necessary data exist. These data are those of Lewis<sup>20</sup> and Cotton.<sup>21</sup> It was pointed out that the agreement is, in fact, striking, with the exception of three cases. Explanation of two of these cases was offered by Cotton on the ground that considerable time had elapsed between the taking of the electrocardiogram and the postmortem examination.<sup>25</sup> It was proposed by Carter and Greene to determine the direction of the electrical axis for this purpose by using the values obtained by the algebraic subtraction of the value of S from that of R in Leads I and III on the ground that these waves represent the opposite effects of the two ventricles in the rotation of the axis. The angle "a" thus obtained is to be regarded as a resultant.

22. Waller, A. D.: Electrical Axis of the Human Heart, *Lancet* **1**:1435 (May 24); 1513 (May 31) 1913.

23. Fahr, G.: Clinical Application of Electrocardiography, *J. Mich. M. S.* **17**:10 (Jan.) 1918.

24. Fahr, G. F.: Principles of Electrocardiography, *Arch. Int. Med.* **27**: 126 (Jan.) 1921.

25. Stewart, H. A.: Experimental Contribution to Study of Cardiac Hypertrophy, *J. Exper. M.* **13**:187 (Feb.) 1911.

This attempt at a quantitative estimation of the electrocardiographic evidence was criticized by Pardee,<sup>26</sup> who concluded that either of two empirical formulas gave the results nearer to the weight ratios. The first of these formulas was used by Lewis in arranging his electrocardiographic findings in the cases in which he had obtained the ventricular weight ratios, at a time when attention had only recently been drawn to the electrical axis. The second is that offered by White and Block.<sup>27</sup> These formulas are essentially similar. Pardee's conclusions were based on the ground that the Lewis and White formulas misplace fewer cases in the weight ratio series. The results are shown graphically in a chart (Fig. 1). This figure is misleading, however, because the weight ratios are represented on one scale, the figures obtained by the formulas on another and the angle "a" on a third scale, so that the results are not comparable.

Examination of Lewis' formula shows that it cannot under all circumstances give a figure representing the electrocardiographic findings. The formula is:

$$(13) R_1 - R_s + S_1 - S_3 = \text{index.}$$

This index is 0 when the angle "a" as determined by Carter and Greene is 60 degrees and also when it is — 120 degrees. For instance, suppose  $R_1 = 12$ ,  $S_1 = 5$ ,  $R_s = 10$ ,  $S_3 = 3$  ("a" = 60 degrees); and in a second case  $R_1 = 4$ ,  $S_1 = 10$ ,  $R_s = 2$ ,  $S_3 = 8$  ("a" = — 120 degrees). In both cases the index is 0. However one determines the angle "a," it is evident that Lewis' figure fails to show the complete reversal of the electrocardiographic data. In general, Lewis' formula gives a high positive figure with left ventricular preponderance and a negative figure with preponderance of the right chamber. A further example of the possible discrepancies may be given from our records:

Case No.	$R_1$	$S_1$	$R_s$	$S_3$	Lewis' Index	"a"
2314	12.0	0.	4.0	1.5	9.5	+ 39°
2237	7.0	3.0	1.5	6.5	9.0	— 40°

Here, again, the electrocardiographic evidence is certainly not expressed by Lewis' index.

The occurrence of waves of large amplitude in cases of left or right ventricular preponderance is pointed out by Pardee. In the case of left-sided preponderance, the largest waves are all  $R_1$  or  $S_3$ , while for preponderance of the right ventricle these are  $S_1$  or  $R_s$ , facts to be expected on the ground of Lewis' explanation of the electrocardiogram as a summation of separate, largely opposing elements due to the spread of the excitation wave through the left and right ventricle

26. Pardee, H. E. B.: Determination of Ventricular Preponderance, *Arch. Int. Med.* **25**:683 (June) 1920.

27. White, P. D., and Bock, A. V.: Electrocardiographic Evidence of Abnormal Ventricular Preponderance and of Auricular Hypertrophy, *Am. J. M. Sc.* **156**:17 (July) 1918.



respectively.<sup>9</sup> It seems impossible that consideration of the deflection in one lead alone can be of value, since, for instance, a high  $R_1$  of given value, has an entirely different significance in conjunction with a negative value in Lead III from that which it has with a positive value in Lead III.

In view of the basis described for the use of the electrical axis in estimating ventricular preponderance, it does not seem that the method should be discarded because of the discrepancies in the series of fifteen cases referred to above.

#### AURICULAR HYPERTROPHY

There is suggestive evidence that hypertrophy of the auricles is sometimes associated with "P" waves of increased amplitude.<sup>27</sup> In estimating the height of the "P" wave the manifest value should be used because of the influence of the direction of the axis on the length of the lead values. In connection with the value of "P" in Lead I, Table 2 can be used for this purpose.

Space does not permit the analysis, but it can readily be appreciated that an understanding of the principles of the electrical axis is essential to the intelligent interpretation of split and bizarre complexes, and of the curves of premature systoles and bundle branch blocks.

#### SUMMARY

1. The definition of the electrical axis is repeated and the various methods proposed for evaluating the angle " $a$ " are outlined.

2. That the angle " $a$ " depends upon the ratio between any two leads is demonstrated and tables for the direct determination of the angle " $a$ " and the manifest value, with a graph for finding the angle by inspection are given.

3. As evidence of the fundamental importance of the electrical axis its relations to the effects of respiration, the position of the body and other causes of displacement of the heart, on the electrocardiogram are pointed out.

4. The use of the angle of the electrical axis at the instant of greatest potential difference in estimating ventricular preponderance is discussed. As far as our knowledge at present goes, this angle probably gives the most accurate indication of the condition present.

Acknowledgment is made of the kind supervision of this paper by Dr. E. P. Carter.

## PAROXYSMAL TACHYCARDIA

WITH REFERENCE TO NOMOTOPIC TACHYCARDIA AND THE  
RÔLE OF THE EXTRINSIC CARDIAC NERVES \*

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Of the recognized disorders of the cardiac mechanism, none possess greater interest than the paroxysmal tachycardias. This affection has been recognized as a clinical entity for more than thirty years, and the condition has been produced experimentally by various means. Two questions have recently been revived; one, concerning sites of origin, especially the possibility of a paroxysm arising at the sinoatrial node (nomotopic tachycardia) and the other, concerning the rôle of the extrinsic nerves of the heart. Herewith I wish to report six cases<sup>1</sup> of paroxysmal tachycardia which illustrate the moot points and the variety of clinical conditions in which the disorder occurs.

### REPORT OF CASES

CASE 1.—J. W., aged 19 years, student. This patient was first seen Dec. 30, 1919, when he came for examination because of unduly rapid and forceful heart action which frequently occurred following exercise. He says they have been present as long as he can remember, and his mother recalls attacks as early as 5 years when the child often ran to her, frightened because of the abnormal cardiac activity. An aunt has told him that when he was a small boy she had noticed that his heart was extremely rapid when at play. Rarely, pounding of the heart is experienced at night but usually there is no consciousness of the heart except during the attacks. The paroxysms are often related to exercise but from consideration of many attacks it is clear that they are not dependent on the total energy expended but rather follow sudden or spasmodic effort. Attacks have occurred irregularly during gymnasium exercises, following certain maneuvers in military drill, swimming, especially just after plunging into cold water, after a sudden spurt for a car or coughing. But in carefully planned gymnasium work and hard labor in the hay field during the summer the pulse rate does not rise above 80. At the laboratory attacks have followed running up and down stairs but at other times this exercise or hopping until dyspnea necessitated rest did not bring on a paroxysm. The emotional factor is seen in the occurrence of paroxysms while dancing and while watching an exciting football match. These attacks always begin suddenly and cease abruptly; according to the patient, "it is just like shifting gears on a car." The duration is from a few minutes to two hours. He thinks he often stops an attack by holding his breath or throwing himself suddenly across a bed or convenient object, and says that recently an attack ceased promptly after pressure on the right eyeball. During the attack the heart beats rapidly and

\* From the Electrocardiographic Laboratory of Mercy Hospital.

1. These patients were referred by Drs. J. A. Lichty (Cases 1, 4 and 5), E. M. Frost (Case 2), J. I. Johnston (Case 3), and G. L. Hays (Case 6), to whom I express my indebtedness.

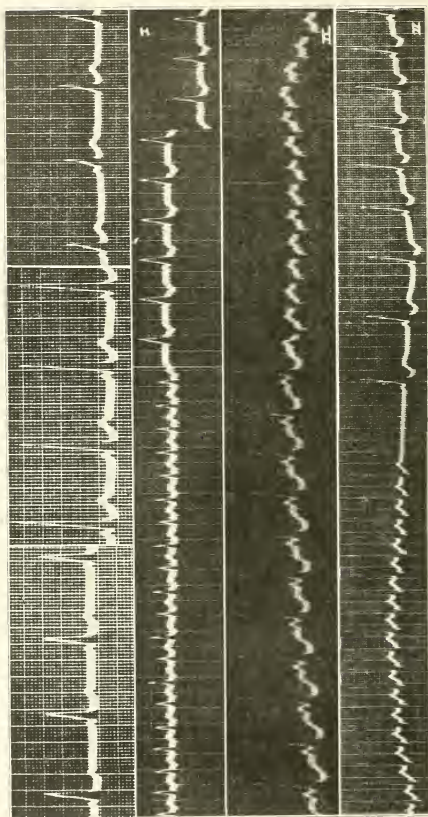


Plate 1.—Illustrating Case 1. Patient's dominant rhythm and records from paroxysm of Dec. 31, 1919. In Lead II the arrow marks the application of pressure on the right vagus.

forcefully; breathing is labored; the skin becomes flushed; he feels very warm, and perspires profusely. Occasionally, there has been pain about the heart.

*Examination.*—April 4, 1920, the patient visited the laboratory. The pulse rate varied from 72 to 80, with sinus arrhythmia; blood pressure, 104/58; skin dry; pupils moderately dilated. After running eight times up and down a flight of twenty-four steps he returned to the laboratory saying "I am winded and it has not started yet." As he sat down the paroxysm began suddenly. Then the following observations were made:

PULSE RATE AND BLOOD PRESSURE OF J. W. (CASE 1) DURING A PAROXYSM

Time	Pulse Rate	Blood Pressure
11:45	74	104-58 (Before exercise)
12:07	184	144-80 (After exercise)
12:10	180	130-74
12:12	180	(Breath held)
12:14	116	115-76
12:19	104	105-75
12:40	106	103-65

The pupils did not show any appreciable change; with the onset of the paroxysm the face became markedly flushed and a drenching sweat supervened. This attack was typical; variation is solely in duration.

*Family History.*—The family history is interesting. The paternal grandfather died suddenly at 48; he is said to have had a "tobacco heart." Three of the four sisters of the father have suffered from toxic goiter. A sister died of tuberculosis.

*Previous History.*—The patient himself has had measles, mumps, chicken-pox and whooping cough when a small boy; diphtheria at 9 years and pneumonia at 13. There is no history of rheumatism or tonsillitis. Growth has been normal and general health has been excellent. There are no abnormal symptoms and the young man leads the life of an active college student, though handicapped by the irregular occurrence of the paroxysms.

*Physical Examination.*—The essential points in the physical examination were: Development and nutrition, good. No gross abnormalities.

*Skin:* Dry. Normal distribution of hair. Dermographia, central red line with a broader zone of blanching on either side.

*Eyes:* Pupils variable, often quite widely dilated.

*Mouth and Throat:* Negative.

*Neck:* No enlargement of thyroid.

*Lungs:* Negative.

*Heart:* Localized apex impulse in fifth interspace. Precordial dulness not increased. Sounds are of good quality and unaccompanied by murmurs. A2 accentuated. Sinus arrhythmia with rate varying between 60 and 90. Blood pressure: systolic, 100-126; diastolic, 58-76.

*Abdomen:* Negative.

*Reflexes.* Normal.

*Fluoroscopic Examination.*—No enlargement of heart. Quick, forceful pulsation, with rather jerky retraction of apex and unusually forceful pulsation of the aorta. Lungs were clear.

Roentgenogram of skull showed no abnormality of sella turcica. Blood cytology: normal. Wassermann reaction, negative. Basal metabolism: normal.

*Reaction to Drugs.*—Atropin, 0.03 gm., rate increased from 60 to 100. The arrhythmia disappeared. In the electrocardiogram the P-R interval remained unchanged; T waves became inverted, returning to upright form in one hour. Pilocarpin, 0.12 gm.; no general reaction. No variations in details not seen normally. Epinephrin, 1 mg. No effect that could be attributed to it.

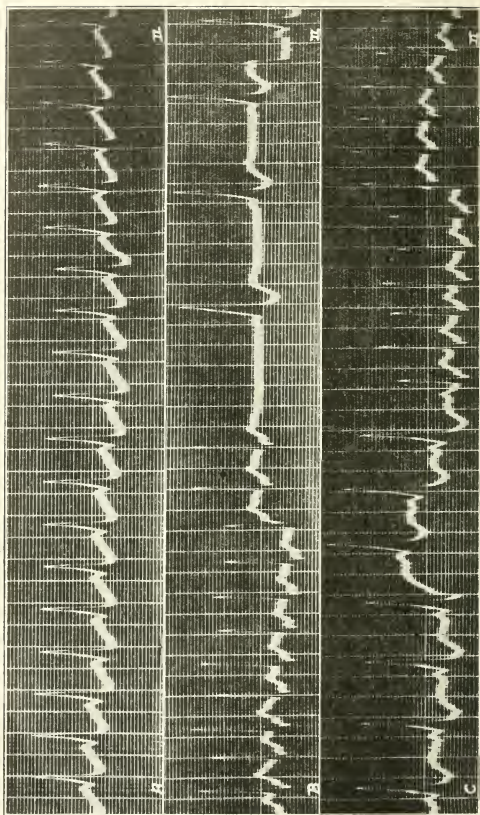


Plate 2.—Illustrating Case 1. From records taken Dec. 17, 1920. A. After exercise, rate 150. B and C are continuous.

*Electrocardiograms.*—The dominant rhythm has always been an A-V arrhythmia: P-R interval, 0.08 second; width of R, 0.12 second; T waves upright. Following exercise, atropin and the paroxysms, the T waves were inverted. The first beat of the paroxysm begins at the end of the normal interval of the fundamental rhythm, with an instantaneous doubling of the P-R interval, halving of the duration of R, and inversion or disappearance of T. The termination of the new rhythm is apparently by the production of a vagus block, prolongation of conduction time and failure of ventricular response. The rate of the paroxysm is from 180 to 195; variation in the R-R intervals occurs and at times is due to variation, amounting almost to alternation, in the P-R interval. The figures in Plate 1 were taken in the latter part of December, 1919. Plate 2 was recorded Dec. 17, 1920.

CASE 2.—A woman, 52 years of age, had suffered for many years from hyperacidity and constipation, associated with alimentary stasis which is the result of marked visceroptosis. The examination of the cardiovascular system is negative, except for the disturbance of the cardiac mechanism. Ectopic beats are known to have been present for the past five years. The first attack of paroxysmal tachycardia occurred in February, 1919. Since then paroxysms have been of frequent occurrence; they often come on in the early morning hours or after meals and have varied in duration from a few minutes to eight hours. Vagus pressure has been tried by several physicians, none of whom have succeeded in stopping the paroxysm by that means. Relief has usually followed emptying the stomach by an emetic. The ectopic beats are seen to arise in the left ventricle. However, the electrocardiogram taken during the paroxysm indicates that the new rhythm arises in the A-V node and that reversal of the mechanism occurs; the type of curve suggests some defect in conductivity of the left branch of the bundle (Plate 3). The illustration was recorded during the afternoon of Oct. 27, 1919. The paroxysm began about 1 p. m. Vagus pressure, aromatic spirits of ammonia, atropin 0.025 gm., and, finally, the passage of a stomach tube failed to arrest the paroxysm, which continued with occasional interruptions by a few normal beats until about 8 p. m. when it suddenly stopped. There was no cyanosis or dyspnea during the attack. The atropin caused marked dryness of the mouth and blurring of vision. Of late there have been no attacks. This is attributed to daily gastric lavage.

CASE 3.—This patient, a single man, aged 24 years, was referred April 6, 1920, with the complaint that on going to bed at night his heart became irregular and rapid, there being a succession of attacks during which the heart suddenly "started up," beat rapidly for a few minutes and then stopped abruptly. There was no pain, no shortness of breath and no symptoms other than the consciousness of the irregularity and this prevented sleep. The condition had been present since his discharge from the army in May, 1919, and was attributed to confinement in an office. He had influenza in January, 1919, while in France.

There has been no loss of weight or strength nor unusual fatigue. He plays volley ball and bowls regularly, without any symptoms referable to the cardiovascular or respiratory system. The hands and feet were often unduly moist, though the skin activity, in general, was not excessive; lacrimation or salivation has not occurred.

The family and the patient's past history are without significance. He has not had either rheumatic fever or tonsillitis. Venereal diseases were denied; the blood Wassermann reaction was negative.

*Physical Examination.*—Development and nutrition, good.

Skin: Generally dry, except the palms which were cold and clammy. Red line dermatographia.

Eyes: Palpebral fissures abnormally wide; pupils dilated. Muscular reactions normal.

Mouth: Teeth good; no apparent pathology in tonsils.

Neck: No enlargement of thyroid.

Lungs: Negative.

Heart: Apex beat in fifth interspace. No enlargement of percussion dullness. Sounds of good quality, without murmurs or abnormal accentuations. Rhythm irregular due to the occurrence of frequent ectopic beats and short paroxysms of tachycardia. The systolic blood pressure varied between 90 and 112 and the diastolic from 60 to 75; during the paroxysms the systolic pressure fell to 80; the diastolic could not be read.

Abdomen: Negative.

Reflexes: Those at elbows and the knee jerks were exaggerated; plantar response, normal.

Blood: Cytology, normal except for a slight leukocytosis, 9,400 present during the second examination which was probably due to recent pharyngitis.

Paroxysms of tachycardia were of frequent occurrence. The taking of the pulse by the nurse or any of the laboratory procedures were sufficient to cause their appearance. They were usually of very short duration, lasting from a few seconds to one half hour, and averaged about 100 cycles. The average rate during the spontaneous paroxysm was 162, with variation of about 0.02 second in the R-R interval. The normal electrocardiogram is that characteristic of excessive sympathetic tone, with relatively large P and T waves and low R. Periods of slow nodal rhythm were seen occasionally. The paroxysms are believed to arise in the A-V node. In Lead I is seen a nodal beat, followed by a beat with a short P-R interval, then P is definitely behind R when the paroxysm begins. At the end of the paroxysm was either a negative P wave or the last beat showed a small upright T and resembled many of the isolated nodal beats (Plate 4).

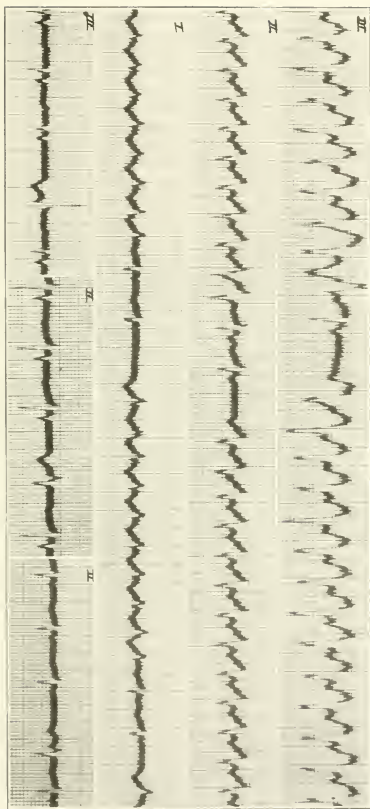
Epinephrin was without any effect, and while pilocarpin produced intense sweating there did not seem to be any specific effect on the electrocardiogram. However, following the injection of 0.03 gm. atropin a paroxysm came on in a few minutes which continued at a rate of 184 during one and one-half hours that the patient remained in the laboratory, and according to him did not stop for four hours.

CASE 4.—A farmer, aged 63, came to the hospital for prostatectomy. When first seen there was an irregularity due to occasional ectopic beats which arose at a low level in the atrium. A similar irregularity of the pulse was noted eight years ago when he had an eye infection. There has been no dyspnea on exertion, no thoracic pain, no edema of the extremities.

*Physical Examination.*—The prominent points of the physical examination were: The face was flushed and there was slight cyanosis of the lips. The lungs showed marked senile emphysema. The heart was not enlarged; there were systolic murmurs at both the apex and over the aortic area: the aortic second sound was accentuated. Blood pressure, 130/80. The first paroxysm was recorded Dec. 3, 1919. When questioned the patient said he had noticed slight discomfort about the heart but thought nothing of it. Subsequently many attacks were observed; it was not unusual for one to begin during a bedside examination. One attack is known to have lasted two hours. The patient was never conscious of the abnormal rhythm and the surgical history was uneventful.

From a comparison of electrocardiograms showing the isolated premature beats and those of the paroxysms, it seemed that the two arose at the same focus. The paroxysm is typical of the atrial tachycardias which arise well below the pacemaker. The illustration was obtained Jan. 24, 1920 (Plate 5, A). Pressure on the right vagus was exerted fourteen cycles before the effect noted. Although the paroxysm soon returned, this is doubtless an example of an ectopic rhythm which was influenced by vagus pressure.

CASE 5.—Man, aged 77 years, whose sole complaint was that he had had a bad taste in his mouth for the past five years. He has been short of breath on exertion for many years, but has never had any edema nor has he been conscious of any abnormal cardiac activity.



\* Plate 3.—Illustrating Case 2. Normal mechanism (Lead II on different days) and paroxysm.



*Physical Examination.*—Skin: Deep cyanosis of lips, tongue and oral mucosa. Lungs: Senile emphysema.

Heart: Slightly enlarged to the left. Systolic murmur heard over entire precordium and transmitted to vessels of the neck. Rhythm, very irregular. Blood pressure, 200/80. Marked thickening of the peripheral vessels.

Abdomen: Liver enlarged and tender to pressure.

Extremities: Negative.

*Fluoroscopic Examination.*—Slight enlargement of heart. Localized enlargement of the arch of the aorta, an exaggeration of the usual senile knuckling. Marked opacity of the aorta.

*Electrocardiogram.*—Shows numerous ectopic beats which arise at two different levels in the atrium and in the left ventricle; also short paroxysms of tachycardia originating at a low level in the atrium. The last two cycles of the paroxysm suggest a shifting of the pacemaker to a higher level in the atrium (Plate 5, B). Because of the short duration of the paroxysms it was not possible to judge the effect of vagus pressure.

CASE 6.—The patient, a woman, aged 58 years, was in the hospital during the week of Jan. 3, 1921, suffering from pain in the lower right quadrant of the abdomen. A mass is said to have been palpated and an exploratory laparotomy advised, but the patient refused operation and left the hospital on the afternoon of January 10. The next morning, about 4 o'clock, she was heard moaning by her niece with whom she was staying. She seemed very weak, was unable to speak for several hours, the pulse was almost imperceptible and the family believed she had suffered a stroke. A physician was called later. He noted the rapid heart action. The following day, January 12, the patient was brought back to the hospital.

*Physical Examination.*—Examination was made at 7 p. m., the principal details of which were: A well developed and well nourished woman, whose appearance when first seen suggested that she was ten years older. She was able to recline without pillows, and was free from pain or any discomfort, except the consciousness of a rapid and pounding heart. The lips and fingers were slightly cyanotic. The lungs were negative; no moisture was present. In the abdomen, the liver edge was palpable, and there was tenderness on pressure over the cecum. The heart was enlarged a little to the left. Both sounds were very weak, unaccompanied by murmurs and without accentuations. The apex rate was 180, and the rhythm was regular, and although the radial pulse was very weak, all beats came through to the wrist. Blood pressure, 95/82. The electrocardiogram showed a regular tachycardia with a rate of 180. The type of curve was supraventricular and from careful examination of a considerable length of record it is believed to have had its origin in the lower part of the A-V node, and that reversal of the mechanism occurred, the P wave appearing as a small notch at the end of R (Plate 5, C). Holding the breath, pressure on the vagus in the neck and on both eyeballs was without any influence whatsoever on the rhythm.

*Clinical Course.*—Morphin was given and the patient rested well throughout the night. At noon, January 13, the apex rate was still 180; blood pressure, 95/75. Crepitant râles were heard at both bases, and the liver seemed larger than on the first examination. There was no dyspnea and she was comfortable except for the palpitation. Tincture of digitalis in 5 c.c. doses was given at 2 and at 4 p. m. Promptly, after the second dose, according to the patient, she vomited a large amount of "bile," the heart suddenly became slower and she dropped off to sleep. When seen at 7 p. m. the improvement in general appearance was quite striking. The pulse rate was 84 and the blood pressure 122/85. The electrocardiogram showed a normal mechanism.

January 15 a short paroxysm was reported but not studied. Examination the following day showed the pulse rate to be 80 and the blood pressure 145/75; the lungs were free from moisture and the liver was not palpable.

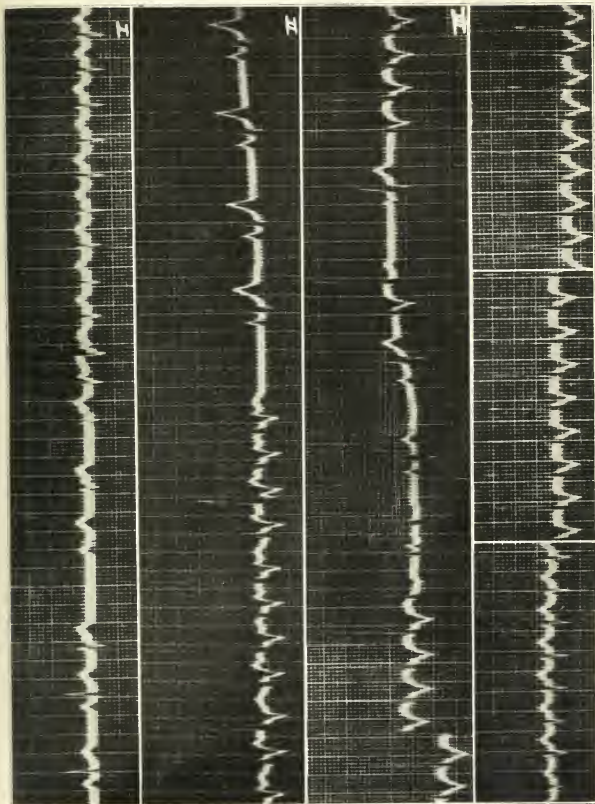


Plate 4.—Illustrating Case 3. Spontaneous paroxysms and paroxysm one hour after 0.02 gm. atropin (fourth line).

Subsequent questioning brought information to the effect that since she was 15 years old the patient had suffered from such attacks which were characterized by very rapid beating of the heart. They frequently came on when at school; at times they were related to fatigue and again occurred during the night. No definite precipitating causes have been known. Fainting often occurred at the onset. Almost invariably the paroxysm has stopped after vomiting. Frequent examinations by numerous physicians have failed to reveal any signs of heart disease and physical and radiographic examinations during the week following the long paroxysm showed no evidence of disease either of the valves or of the myocardium. The previous paroxysm occurred last October. The one described was of the longest duration, having lasted for at least sixty hours.

This case is especially interesting in comparison with the first case cited, and recalls the analogy of Bouveret between epilepsy and paroxysmal tachycardia in that the individual is always under the menace of new paroxysms. The increasing duration of the attacks with the appearance of signs of myocardial failure during the latest one is of prognostic significance.

#### NOMOTOPIC TACHYCARDIA

Lewis<sup>2</sup> has defined paroxysmal tachycardia as an affection in which the heart rhythm (sino-atrial nodal rhythm) becomes submerged and the heart responds to impulses formed at a more rapid rate in some other portion of its walls. Such a definition precludes the conception of a nomotopic tachycardia and the later statement that paroxysms arising in the sino-atrial node have not as yet been identified follows as a corollary. Likewise, Mackenzie<sup>3</sup> states that paroxysmal tachycardia is a term to indicate the starting of the heart's contraction at an abnormal focus with a sudden increase in the rate of the heart. Donzelot,<sup>4</sup> in a study of the pathology of paroxysmal tachycardia, has included all exaggerated accelerations of the heart which begin and end abruptly. His classification embraces: (a) Regular paroxysmal tachycardia, which results from displacement of the stimulus, though he says it is possible to conceive the existence of a paroxysmal tachycardia, "nomotope," but "heterotype." (b) Auricular tachysystole, atrial flutter. (c) Irregular paroxysmal tachycardia, atrial fibrillation. Wenckebach has described nomotopic tachycardia and recently G. Galli<sup>5</sup> reported a case with polygraphic records which he believed arose in the normal pacemaker, and has argued for nomotopic paroxysms of neurogenic origin. Certain of his theses are worthy of criticism: I and IV. If vagus pressure is sufficient and prolonged it is usually successful in stopping the paroxysm: the Valsalva experiment reduces the

2. Lewis, T.: *The Mechanism and Graphic Registration of the Heart Beat*, New York, Paul B. Hoeber, 1920.

3. Mackenzie, J.: *Principles of Diagnosis and Treatment in Heart Affections*, London, Oxford Press, 1916.

4. Donzelot, E.: *Les Tachycardies Paroxystiques: Etude Pathogénique*, *Ann. de méd.* **11**:155, 1914.

5. Galli, G.: *Sur les Mécanisme de Terminaison et de Début des Accés dans la Tachycardie Paroxystique (Nomotope)*, *Arch. d. mal. du coeur* **12**:289, 1919.

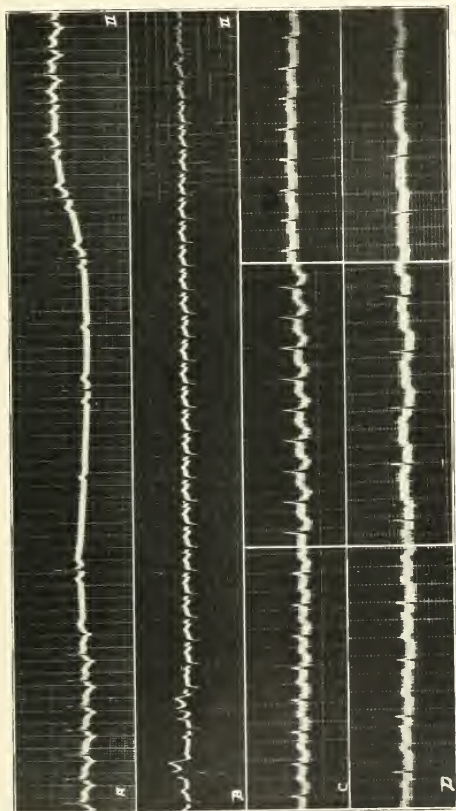


Plate 5.—A. Illustrating Case 4. Right vagus pressure applied fourteen cycles before first normal beat. B. Illustrating Case 5. C. Illustrating Case 6. About thirty-six hours after onset of paroxysm. D. Twenty-seven hours later, three hours after termination of paroxysm.

frequency of simple tachycardia and often arrests a paroxysm: those tachycardias not thus relieved are of heterotopic origin. The failure of vagus pressure on the basis of inadequate stimulation is difficult to answer. Surely but few continue vagus pressure for thirty minutes. The common practice is to apply pressure until the heart action is altered or the discomfort produced demands its discontinuance. It is the usual experience of those who resort to this procedure that in some cases it is apparently successful while in others there is no effect. In Case 1 of the present series the effect of vagus pressure was doubtful and in the case of Carter and Wedd<sup>6</sup> no pressure that could be endured influenced the paroxysm. On the other hand, there are numerous records of unquestioned heterotopic tachycardias which are definitely affected by stimulation, for example, Case 4. In Case 3 the patient had long successfully practiced the Valsalva experiment, but the effect of vagus pressure is difficult to interpret because of the recurring short paroxysms, and the fact that there was no change in the electrocardiogram. III. Atropin in sufficient dosage may induce a paroxysm of tachycardia. It did in Case 3, but the paroxysm arose at the A-V node, not the sinus node. V. An emotion may bring forth a paroxysm. But again, it may be a heterotopic rhythm, as in Case 3. VII. There occurs at times an abrupt passage from normal rhythms to that of simple tachycardia. This presupposes proof of the exact nature of both phases. From observation alone of the movements of the galvanometer string during the paroxysm in Case 1 that seemed to occur, but examination of the record showed that without any pause, the change in rate from 115 to 188 followed a shift of pacemaker to a higher level in the auricle, with prolongation of A-V conduction and other changes in the electrocardiogram. X. Rhythmic oscillations may occur during a paroxysm; this is characteristic of sinus activity. The slow mechanism in Case 1 is an A-V arrhythmia. It is not possible to deny that fluctuation might occur in nodal tachycardias, though this rarely, if ever, occurs in any marked degree. VIII. The electrocardiogram usually shows a negative P wave and shortened conduction time: but P is not always inverted even in cases of evident nodal rhythm: moreover the eye accustomed to the perusal of electrocardiograms may be occasionally deceived, and finally the electrocardiogram is often difficult to interpret and ambiguous. All this is admitted, and likewise the conclusion that because the electrocardiogram shows most tachycardias to be heterogenetic, it is unjust to insist that only extrasinusal tachycardias may occur. However, when the electrocardiogram fails to

6. Carter, E. P., and Wedd, A. M.: Report of a Case of Paroxysmal Tachycardia Characterized by Unusual Control of the Fast Rhythm, *Arch. Int. Med.* **22**:571 (Oct.) 1918.

show the origin of the rhythm, to what shall one turn? Polygraphic records may be more simple of interpretation, but who shall vouch for their authority?

Shortly after the appearance of the paper by Galli, a case of paroxysmal tachycardia was reported by Boden<sup>7</sup> in which during the paroxysm, the P wave of the electrocardiogram was similar to that in the normal, but with an increase in negativity in the ventricular complex. After atropin the electrocardiogram was exactly like that during the paroxysm, though the rate increased to only 144 while that of the paroxysm was 170. This was interpreted as a case of nomotopic tachycardia resulting from dominance of the accelerator system. In the discussion of the case of paroxysmal tachycardia with voluntary control reported by Carter and Wedd, while the term nomotopic was not used, it was stated that there could be no ectopic focus wholly removed from neurogenic control which was responsible for the fast rhythm. More recently White<sup>8</sup> has considered this subject in a study of a case in which there were short "paroxysms," but no abrupt onset or offset in the rapid rhythm. The P wave remained upright and fell back on T and there were slight variations in the intervals between beats at the height of the paroxysm, the maximum rate of which was about 188. This was called "paroxysmal tachycardia, arising in or very near the sino-atrial node and not showing an absolutely abrupt onset or offset." From the definitions given and the work cited the existing confusion is apparent. In the light of Lewis' later work, closer relations between extra-systoles, paroxysmal tachycardia, flutter and fibrillation are indicated, and it may well be that Donzelot in his clinical classification five years ago wrote better than the experimental knowledge of the time warranted. But to introduce as a paroxysmal tachycardia an altered mechanism which is neither heterogenic, ectopic nor paroxysmal in the common clinical meaning of having an abrupt onset and offset, is to further complicate the situation by bringing into the category simple tachycardias.

As to the nature of paroxysms of tachycardia, the conclusion is inevitable (Lewis) that the paroxysm is composed of a series of extra-systoles. Extrasystoles definitely known to arise in either the S-A or A-V node are rare, though their possibility or existence is not denied. (The term "extrasystole" is here used following the terminology of Lewis. Theoretically, the only true extrasystole not an ectopic beat is an interpolated sinus extrasystole. Inasmuch as practically all so-called

7. Boden, E.: Über den Einfluss der langen Herznerven auf die Form des Elektrocardiogramms in einen Fall von Paroxysmaler Tachycardie, Deutsch. Arch. f. klin. Med. **130**:249, 1919.

8. White, P. D.: Clinical Observations on Unusual Mechanisms of the Auricular Pacemaker, Arch. Int. Med. **25**:420 (May) 1920.

extrasystoles are in reality ectopic beats, it would simplify a discussion of heterogenetic impulses and clarify their inter-relation if the former term could be dropped from the literature.) The occurrence of ectopic beats in the tachycardias under consideration may be mentioned at this point. In Case 1 no isolated abnormal beats have ever been seen. In Case 2 ectopic beats arising in the left ventricle have been frequently recorded; the paroxysm, however, was probably of supraventricular origin. Nodal beats were frequent in Case 3 and often occurred in pairs. In Case 4 ectopic beats arising at a low level in the atrium were constantly present, often giving rise to a coupled rhythm and from the conformation of the curves it appeared that the paroxysm arose at the same focus. In Case 5, although both ventricular and atrial ectopic beats occurred, the only paroxysms recorded were of the atrial type. No ectopic beats have been noted in Case 6, but the patient was under observation only ten days. Paroxysms which arise in the A-V node are known. Case 3 affords another example. There is no difficulty in this case, likewise in Cases 4 and 5, in seeing the paroxysm as a succession of extrasystoles. If extrasystoles can occur in the sinus node what is there to prevent a series of them? And if increased irritability may occur abruptly in the A-V node resulting in a succession of beats that constitutes a paroxysm, what prevents such an accident at the sinus node? Doubtless the more complete, at least better known, regulatory mechanism at the sinus node is an important factor.

In any criteria for paroxysmal tachycardia it would seem well to insist that the essential characteristic of the new rhythm shall be its abrupt onset and termination. A recent observation is that of a woman of 50 years of age who had had a finger nail removed, with cocaine for the local anesthetic. Following the operation the pulse rate increased to 160 and she thought that the rapid and forceful heart action came on suddenly as she was being helped into bed. The cardiac mechanism was watched with the galvanometer for two hours. The electrocardiogram at this time and later showed that the rapid rhythm arose at the sinus node. The systolic pressure varied between 200 and 185 and the diastolic remained at about 110. From subsequent observations it appeared that the normal pressure was 150/85. The rate remained quite constant for about three hours; vagus pressure produced temporary slowing but did not break the rhythm. It seemed for a time as though this might be a sino-atrial paroxysmal tachycardia, but after four hours the rate was 140 and after six hours 120; the next morning it was 100, and during the two following days varied between 80 and 124. In experimental accelerator stimulation sino-atrial rates from 150 to 250, and occasionally higher, have been obtained. In Case 1 the nodal rhythm following exercise reached the rate of 150. The par-

oxysms reported showed rates varying between 120 and 195. It is not necessary to consider any rhythm which shows neither displacement of the stimulus nor an abrupt beginning or ending as other than a simple tachycardia. Rate alone can have no place as a criterion for paroxysmal tachycardia.

The difficulties of establishing a nomotopic paroxysm by means of the electrocardiogram are manifold. It is necessary to consider, and to differentiate, if possible, not only the intrinsic changes that may accompany the new rhythm but changes that may be due to increase in rate, stimulation of the cardiac nerves or changes in chemical environment, associated with or dependent on either of the foregoing.<sup>9</sup> No analysis of the paroxysm is reliable unless the onset and termination have been recorded. The record of Boden is wanting in this respect. That of Galli need not be considered because of the inadequacy of polygraphic records. In Case 2, if one were to consider only the fully developed new rhythm, especially Lead II, it would not be difficult to establish a nomotopic tachycardia; the wave preceeding R could be regarded as P and the conduction time would be normal; the small thickening after R would be called T and the diminished size, likewise the notching and the widening of R would be attributed to alteration in nerve control or chemical environment. But the facts that after a brief respite the paroxysm invariably begins without an atrial wave, and that the definite wave between the spikes spaces accurately as a T wave, cannot be dismissed. Another possible interpretation is that the paroxysm arises in the upper part of the right branch of the bundle and independent atrial contractions occur at the same rate. But from consideration of all the facts, a nomotopic tachycardia is impossible. In Case I there is an abrupt onset of a rapid rhythm apparently with displacement of the pacemaker to a higher level, lengthening of A-V conduction from 0.08 to 0.16 second, a lower and narrower R wave and absence of T. As has been noted, the paroxysm of tachycardia is but one feature of a temporary but profound sympathetic stimulation. This question arises, are these changes in the electrocardiogram specific for the new rhythm, or are they the result of sympathetic stimulation acting on the original rhythm, an exaggeration of those seen after the earlier exercise. The inversion and disappearance of T has been seen before; the lowering of R and shortening of ventricular response may be due to the increase in rate. Sympathetic stimulation tends to decrease A-V conduction and increase in rate to prolong it. The fact that the conduction time in this first cycle is practically double that of the preceding is significant and the later lengthening may be associated with increased rate. If as

9. Mines, G. R.: On Dynamic Equilibrium in the Heart, *J. Physiol.* **46**: 349, 1913.



Lewis says the changes seen during the paroxysm are an intrinsic part of the new mechanism then this is a new rhythm arising at a higher level in the atrium and details suggest that its origin may be the S-A node. In the absence of authoritative criteria nomotopic paroxysmal tachycardia cannot be proved in clinical electrocardiograms, but to deny the possibility of the same is to deny to the sinus node properties of irritability and rhythmicity present in the A-V node, also a homogenetic centre, and other loci in the heart where these functions are normally present in less degree, and surely this requires proof.

#### THE RÔLE OF THE EXTRINSIC NERVES

The relation of the extrinsic nerves to cardiac irregularities has been extensively investigated. The attempt to control paroxysms of tachycardia by vagus pressure has long been practiced. The actual effects are debatable. While there are those who believe the procedure infallible, according to Lewis either there is no effect or the new rhythm abruptly ends and the normal rhythm is resumed. In Case 1, in which vagus control might be expected, on one occasion the paroxysm stopped twenty cycles after the application of pressure; prolongation of conduction and failure of ventricular response occurred, a common result of vagus stimulation. But at another time the paroxysm terminated in an exactly similar way when no pressure was used and the patient made no effort to stop the paroxysm. The same mechanism was seen for the third time, when the individual held his breath to stop the attack. In the case of Carter and Wedd, likewise a possible nomotopic tachycardia, there was lengthening of the P-R interval of the last cycle and failure of ventricular response terminated the paroxysm, although this could not be brought about by vagus pressure. It would seem in these two cases, both of which were due to predominant accelerator action, as though the normal rhythm was restored by a resumption of vagal tone, but that this did not occur as the result of interference from without. In Case 3, in which the paroxysms were definitely of sympathetic origin, one paroxysm continued for fifty-nine beats, being of longer duration than many, and ended abruptly without any change in the electrocardiogram. In Case 4, an atrial tachycardia, vagus pressure did apparently break the ectopic rhythm by the production of block.

The accelerator system has likewise received much attention. Bouveret<sup>10</sup> in 1889, from two cases of his own and from similar ones in the literature, described the malady that has since borne his name, essential paroxysmal tachycardia, which occurred in individuals said to be free from any disease of the heart, thyroid or central nervous system.

10. Bouveret, L.: *De la Tachycardie Essentielle Paroxystique*, Rev. de méd. 9:753, 1889.

Because of normal findings in the intervals between attacks he argued that the trouble must come from a profound disturbance in the innervation of the heart and believed that the mechanism was by excitation of the accelerator nerves, probably in the intracardiac ganglia. The etiology included a combination of physical and cerebral causes; physical fatigue, emotion and sense of cold were given as precipitation causes of the paroxysms. Rothberger and Winterberg,<sup>11</sup> studying the effect of stimulation of the accelerator nerves and sympathetic ganglia, found the usual reaction to be a simple tachycardia with characteristic changes in the electrocardiogram; in one instance after stimulation of the left accelerator a negative atrial wave appeared without increase in frequency; following simultaneous stimulation of both accelerators T almost entirely disappeared and when present was a negative wave. In a later work they produced a heterotopic tachycardia by sympathetic stimulation in a heart previously treated with barium chlorid. Donzelot reported extrasinusal or heterotopic tachycardias from stimulation of the left stellate ganglion. Levy<sup>12</sup> has shown the occurrence of ectopic ventricular beats after accelerator stimulation in cats which were under light chloroform anesthesia. Clerc and Pezzi<sup>13</sup> obtained heterotopic tachycardias arising in various levels of the A-V node after excitation of the accelerator nerves, but instead of faradic stimulation, they resorted to strontium chlorid and nicotin for exciting agents. The conclusion of Lewis from his consideration of experimental and clinical cases is that it has not been shown that abnormal nerve impulses playing upon a normally nourished heart may be responsible for extrasystoles or higher types of disorders, but that nervous impulses playing upon an irritable heart may provoke such reactions.

Galli<sup>14</sup> recently reported a case in which paroxysms are said to have come on after atropin, and which he believed to be conclusive evidence of vagus control of the paroxysm. Lewis emphasizes the fact that this occurred in a patient subject to paroxysms. Moreover, in this case the small dose of atropin generally given and the delayed response cast some doubt on the atropin effect. One mg. hypodermically is a small dose, and the tachycardia did not develop for forty-three minutes. The atropin effect ordinarily has begun to wear away by this time. The only convincing record is that in his Figure 5, in which the paroxysm came on fifty minutes after the administration of 30 drops by mouth

11. Rothberger and Winterberg: Ueber die Beziehungen der Herznerven zur Form des Elektrokardiogramms, *Arch. f. d. ges. Physiol.* **135**:500, 1910.

12. Levy, A. G.: The Exciting Causes of Ventricular Fibrillation in Animals under Chloroform Anesthesia, *Heart* **4**:319, 1912.

13. Clerc, A., and Pezzi, C.: Le Rythme Septal du Coeur, *Arch. d. mal. du coeur* **13**:103, 1920.

14. Galli, G.: Attacks of Paroxysmal Tachycardia Following Atropin, *Heart*, **7**:111, 1920.

and persisted for two and one-quarter hours, and here it is the comparative duration that is important. In Case 3 of this series shortly after the administration of 2 mg. atropin a paroxysm occurred at a higher rate than the spontaneous paroxysms, and persisted without interruption for four hours, during which time no usually successful maneuvers would stop it. The higher rate in this paroxysm may have been due to the fact that although the spontaneous paroxysms resulted from heightened accelerator action the vagus still exerted some influence, which was removed by atropin. That a slight mental disturbance occurred may have indicated unusual susceptibility to this drug, but the cardiac response was such as to leave no doubt that the abolition of vagus tone was a definite factor in the long paroxysm.

The position of Lewis, which postulates an underlying toxemia rendering the heart abnormally susceptible to unusual activity of the extrinsic nerves, is incontrovertible, for who can prove that there is no subtle poison at work. It remains to inquire into the possible nature of the toxins. Danielopolu,<sup>15</sup> accepting the doctrine that paroxysmal tachycardia cannot originate in an intact myocardium, described an interesting case of exophthalmic goiter in which there were paroxysms of tachycardia associated with unilateral exophthalmos. According to his explanation, simultaneous stimulation of both accelerators occurred, that of the right gave rise to the exophthalmos and the left, to a heterotopic tachycardia. For the latter he assumed a lesion in the bundle of His which was in a hyperexcitable state and the toxic product of the thyroid gland acted as the exciting agent. A few cases of paroxysmal tachycardia have been reported in which histologic findings were negative, and in the case of thyroid disease it does not appear necessary to presuppose an organic lesion; moreover, this is unlikely in the early stages of the disease. Besides the affections attributed more or less definitely to the thyroid there remains the entire gamut of disorders of the autonomic nervous system. Cases 1 and 3 of this series hardly fit into any of the groups included under exophthalmic goiter or in that of the irritable heart, nor is there sufficient reason to believe that early organic heart disease exists. In the first case the paroxysm is only an incident in the violent reaction to sudden sympathetic stimulation; the drenching sweats are the outstanding feature for the patient. In the other case, the dilated pupils, sweating palms, dermatographia and unstable cardiac mechanism constitute a familiar clinical picture, of which the paroxysms so easily provoked are only a part. But these individuals belong somewhere among the confused syndromes called

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15. Danielopolu, D.: Accès de Tachycardie Paroxystique avec Exophthalmie Unilaterale chez une Ancienne Basedowienne. *Compt. rend. Soc. de biol.* **79**: 103, 1916.

endocrinopathies. It is hardly advisable to emphasize Case 6 in this connection, except to recall that there is a definite history of paroxysms of tachycardia extending over a period of forty-three years and that even today there is no demonstrable evidence of heart disease in the usual meaning of that term, and to suggest that this patient belongs to the same group. In such conditions is not the consideration of toxic substances rendering centers abnormally susceptible to nervous influence which precipitate the disturbances merely calling one thing by two names, or perhaps attempting to push the question further back into the chemical pathology of the autonomic system? And may it not be that when this pathology shall be understood, there will stand one group of paroxysmal tachycardias due to faulty nervous control as Bouveret has written, the fault being whatever may come to be recognized as pathologic in the autonomic nervous system?

#### SUMMARY

Six cases of paroxysmal tachycardia are reported. Two are in elderly individuals in whom there are signs of degenerative changes involving the heart and aorta. This is a frequent association and the paroxysms are believed to be expressions of high irritability in inflammatory foci in the muscle wall. A third case is an example of a group of paroxysmal tachycardias that are usually considered to be of reflex origin. The visceroptosis and alimentary stasis are of long standing. The recent appearance of paroxysms where formerly ectopic beats alone occurred indicates an altered response on the part of the heart. The direct relation between the paroxysms and the alimentary condition is apparent and suggests that the paroxysms are analogous to those produced by ligation of the coronary arteries; because of mechanical displacement embarrassment of the coronary circulation results and there may have occurred changes in the heart muscle, not detectable by physical signs, which render the myocardium less tolerant of interference with its blood supply. Three of the cases seem to fulfill the requirements of the "maladie de Bouveret." There is no evidence of organic heart disease, nor of Graves' disease or so-called hyperthyroidism. The two young men are suffering from some disorder of the autonomic nervous system in which transient predominance of the accelerator division frequently occurs. In this connection the rôle of the extrinsic nerves of the heart in paroxysms of tachycardia has been considered, and it is believed unnecessary to postulate the existence of an underlying toxemia which renders the heart abnormally susceptible to nerve impulses, for both of these factors may well be one and the same thing, and it is hardly necessary at present to attempt to differentiate neuro- from chemical pathology in the autonomic nervous system.

Concerning nomotopic paroxysmal tachycardia there is much confusion in the literature and the most authoritative definitions of paroxysmal tachycardia do not include even the possibility of its existence. It is suggested that the first requirement of any paroxysm shall be an abrupt onset and termination. The necessity of recording the onset of a paroxysm for its correct analysis has been pointed out. In the first case reported, in which the dominant rhythm has its origin in the A-V node, with the onset of the paroxysm there was a sudden shifting of the pacemaker to a higher level in the atrium and from the character of the electrocardiogram the new rhythm might have originated in the S-A node. However, nomotopic tachycardia cannot be established by clinical electrocardiograms. Paroxysms of tachycardia are now regarded as successions of extrasystoles. The existence of sinus extrasystoles is recognized. But even in the absence of demonstrable relationship between such beats and the paroxysm in any given case the negation of the possibility of a nomotopic paroxysmal tachycardia does not seem justifiable.

# IRON AND ARSENIC AS INFLUENCING BLOOD REGENERATION FOLLOWING SIMPLE ANEMIA

## VI. NEGATIVE INFLUENCE OF FAMILIAR DRUGS ON THE CURVE OF HEMOGLOBIN REGENERATION FOLLOWING HEMORRHAGE \*

G. H. WHIPPLE AND F. S. ROBSCHUIT

SAN FRANCISCO

Is iron of value in the treatment of anemia? Is iron absorbed from the intestine when given in organic or inorganic form? Such questions lead to fields of discussion over which has risen the smoke of polemics and arguments without end. We believe that some of these difficulties may be cleared away by careful definition of terms. Our experiments deal with secondary anemia due to hemorrhage and not with chlorosis or any other form of anemia. We have controlled certain diet factors which can influence profoundly the hemoglobin regeneration in this form of secondary anemia. We suggest that our critics control these diet factors before any great emphasis is placed upon drug factors. It is now established that diet factors are concerned in the rapid regeneration of hemoglobin, therefore, these facts must be considered in evaluating any reaction in conditions of anemia.

Chlorosis has been mentioned so frequently in this discussion and others that we feel it necessary to state that in our opinion this condition does not belong in this group of simple secondary anemias. Whether this disease reacts favorably to iron therapy is not germane to this discussion. It seems to be a disease which is becoming much less frequent in many communities due to modified dietary or living conditions or other unknown factors. It would be of interest to collect accurate data on the influence of diet factors alone in this disease.

We do not think it is necessary to review the literature of anemia and iron therapy. It may be admitted that we have not tested all the various forms of iron which are being used in the treatment of anemia, but it seems to us that this is not necessary. We are able to show that many of the iron preparations commonly prescribed are inert, or, at least, much less potent than simple diet factors. The burden of proof now rests with those who claim that one or more iron preparations are potent in anemia under controlled diet conditions.

Some experimental work has been done in secondary anemia to show whether or not iron compounds are potent in stimulating the regenera-

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\* From the George Williams Hooper Foundation for Medical Research, University of California Medical School.

tion of hemoglobin. In much of this work the anemia was produced by drugs which destroy the red cells in the body and leave the freed hemoglobin to be stored or used in any way by the endogenous body mechanism. This type of anemia must not be confused with the type used in our experiments—that is, anemia due to simple hemorrhage. This destruction of red cells in the body may be associated with a storage of hemoglobin radicles somewhere in the body which may be capable of influencing subsequent hemoglobin regeneration. We hope to report on this type of hemoglobin regeneration in the near future.

Arsenicals were used in some of our experiments. It seemed best to include some of this group in this paper because their use in certain forms of anemia is well recognized. Both Fowler's solution and sodium cacodylate are inert under the conditions of these experiments.

Objection may be raised to the use of dogs in these experiments because they are carnivorous animals. The dogs used by us were raised in our kennels and have been omnivorous since weaning. The diet on which they thrive is a mixture of food scraps obtained from the University Hospital. It contains cooked bones, meat, bread, potatoes, rice, etc. This mixed diet obtains in all resting periods between experiments. Unless otherwise noted, these animals are active, healthy and normal in all respects.

#### EXPERIMENTAL OBSERVATIONS

The general method used in all these experiments has been fully described in the first paper of this series.<sup>1</sup> Unless otherwise stated, the plasma volume has been directly determined by the nontoxic dye, "brilliant vital red."<sup>2</sup> This dye has been furnished us through the courtesy of Dr. H. M. Evans of the department of anatomy, and we are indebted to him for much advice and council. The blood is received into isotonic sodium oxalate solution, and the ratio of cells and plasma is determined in calibrated centrifuge tubes. The hemoglobin is determined by a modification of the Palmer method described recently by one of us (F.S.R.).<sup>3</sup> Red and white counts are made in the usual manner from blood obtained by venous puncture. For other details of this work, we refer the reader to the first paper of this series.<sup>1</sup>

Paper V of this series<sup>4</sup> records many experiments in which Blaud's pills were added to various diets. We wish to refer to this paper for the details of these experiments. Blaud's pills were inert under these experimental conditions. It seemed necessary to test out other drugs

1. Whipple, Hooper and Rabscheit: *Am. J. Physiol.* **53**:151, 1920.

2. Hooper, Smith, Belt and Whipple: *Am. J. Physiol.* **51**:205, 1920.

3. Rabscheit: *J. Biol. Chem.* **41**:209, 1920.

4. Hooper, Rabscheit and Whipple: *Am. J. Physiol.* **53**:263, 1920.

under these same conditions, and the charts giving these data are given below.

TABLE 82.—BLOOD REGENERATION—FERRIC CITRATE  
Dog 18-114. Bull mongrel. Female. Adult

Date, 1920	Pigment Volume Hb. per Cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
7/ 8	2,078	C.e. 1,625	C.e. 754	C.e. 854	% 52.4	% 128	0.72	8,8	12,4	Kg. 12.25	C.e. 132	
7/ 8	Diet: Bread and milk											
7/ 9	Bled 406 c.c.											
7/10	Bled 406 c.c.											
7/12	805	1,262	902	348	27.6	64	0.82	3.9	8.2	11.95	105	
7 12	Diet: 150 gm. bread, 500 c.c. milk, 1 c.c. of 5% solution of ferric citrate subcutaneously daily											
7/20	1,188	1,383	858	491	35.5	86	0.94	4.6	12.2	11.95	115	
7/28	1,215	1,580	896	520	37.6	88	0.80	5.5	9.8	11.70	118	* Slight
8/ 3	1,225	1,846	822	523	39.0	91	0.79	5.8	9.0	11.50	116	* Slight
8/13	1,130	1,410	846	544	38.5	80	0.73	5.6	8.2	11.65	121	* Slight
8/20	1,244	1,325	768	574	43.3	101	0.85	6.0	7.4	11.35	117	* Slight
8/27	1,493	1,440	772	646	44.9	104	0.84	6.2	11.0	11.20	128	* Slight
9/ 3	1,428	1,498	850	629	42.0	95	0.75	6.3	10.4	11.05	135	* Poik.
9/10	1,405	1,388	774	599	43.2	101	0.80	6.3	8.4	10.65	130	* Poik.
9 10	Diet: Mixed, with extra food. (No ferric citrate given)											
9/17	1,693	1,693	985	691	40.8	100	0.73	6.9	6.4	13.55	125	* Poik. +†
9/24	1,653	1,798	1,053	722	40.1	92	0.73	6.3	6.8	15.10	120	* Poik. +†

\* Poikilocytosis of red blood cells.

† Food poor in meat.

Table 82 shows the curve of blood regeneration of a standard dog on a bread and milk diet given ferric citrate subcutaneously. It may be stated that the same reaction would be expected in the same dog under identical conditions without the ferric citrate. We can refer to other experiments on this same dog which show the expected favorable and rapid blood regeneration on diets of meat and liver. Table 49 of this series <sup>5</sup> shows the curve of blood regeneration on a diet of cooked meat scraps. The return to normal was almost complete in three weeks. Also Table 61 of this series <sup>6</sup> shows the curve of blood regeneration on a diet of cooked beef liver. The return to normal was complete in two weeks and somewhat above the initial level in three weeks.

This favorable blood regeneration on this diet of meat or liver is in contrast to the slow reaction expected on bread and milk or actually recorded in Table 82 with bread and milk plus ferric citrate.

5. Whipple, Robscheit and Hooper: Am. J. Physiol. **53**:238, 1920

6. Whipple, Robscheit and Hooper: Am. J. Physiol. **53**:252, 1920.



Several interesting points in this experiment should be noted. The blood per kilo is a very high figure, on the average. This is usually found in very active dogs which are somewhat below normal in weight. This dog lost some weight during the bread and milk feeding and the plasma volume likewise decreased as is common under such conditions. This accounts, in part, for some of the increase in red hematocrit and hemoglobin, but is more accurately evaluated in the pigment volume figures. When the dog is put on forced feeding, there is a remarkable gain in weight and plasma volume and an actual fall in red hematocrit and hemoglobin. The pigment volume, however, shows the true values for hemoglobin production. A hasty survey of these figures might lead one to erroneous conclusions unless the facts as given are carefully weighed. This type of experiment shows, too, the necessity of blood plasma measurements.

TABLE 83.—BLOOD REGENERATION—FERRIC CITRATE  
Dog 19-95, Bull mongrel, Male, Adult

Date, 1920	Pigment Volume Hb. per cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	R. B. C. Million	W. B. C.	Weight	Blood per Kilogram	Remarks
7 8	1,570	C.c. 1,412	C.c. 734	C.c. 644	% 45.6	% 111	0.79	7.0	7.4	Kg. 12.25	C.c. 115	* Slight
7 8	Diet: Bread and milk											
7 9	Bled 353 c.c.											
7 10	Bled 353 c.c. No distress											
7 12	722	1,052	741	301	28.6	68	0.86	4.0	11.0	12.05	87	* Slight
7/12	Diet: 150 gm. bread, 500 c.c. milk, 1 c.c. of 5% solution ferric citrate subcutaneously daily											
7/20	1,133	1,295	814	469	36.2	87	0.87	5.0	12.2	11.80	110	* Slight
7/28	1,190	1,264	749	508	40.2	94	0.78	6.0	10.8	11.80	107	* Slight
8/ 3	1,256	1,256	702	542	43.2	100	0.84	6.0	7.2	11.75	107	* Slight
8/13	1,141	1,197	672	513	42.9	95	0.79	6.0	17.0	11.75	102	* Slight
8 20	1,215	1,225	711	502	41.0	99	0.85	5.8	12.0	11.55	106	* Slight
8 27	1,185	1,212	696	505	41.7	98	0.71	6.9	5.8	11.65	104	* Polk. +
9/ 3	1,273	1,303	730	561	43.0	98	0.72	6.8	6.4	11.50	113	* Polk. +
9/10	1,165	1,202	709	481	40.0	97	0.81	6.0	7.2	11.35	106	* Polk. +
9/10	Diet: Mixed, with extra meat. (No ferric citrate given)											
9 17	1,632	1,497	808	674	45.0	109	0.83	6.6	6.6	13.75	109	* Slight

\* Polikilocytosis of red blood cells.

Table 83 shows the influence of ferric citrate given subcutaneously. We are able to refer to other experiments on this same animal which have been published. Table 3 of this anemia series<sup>7</sup> gives the curve of blood regeneration on a mixed diet. It is clear in this experiment

7. Whipple, Hooper and Rohsheit: Am. J. Physiol. **53**:159, 1920.

that blood regeneration was *slow* until meat was added in liberal amounts. The curve of regeneration finally returned to normal. Table 41 gives the blood regeneration curve on a liberal diet of rice, potatoes and milk. It is clear that these curves, if anything, are better than the curve of Table 83. We have established the fact that this rice-potato-milk diet is slightly more favorable for blood regeneration than a simple bread and milk diet.

These control experiments under identical conditions make it clear that the ferric citrate under these experimental conditions is inert. The curve of regeneration has not been influenced by the administration of this drug.

TABLE 84.—BLOOD REGENERATION—OVOFERRIN

Dog 293. Bell Mongrel. Male. Adult

Date, 1920	Pigment Hb. percent Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb	Color Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
7/29	1.588	C.c. 1,495	C.c. 796	C.c. 715	% 47.8	% 106	0.77	6.9	7.6	Kg. 13.90	C.c. 110	* Slight
7/29	Diet: Bread and milk											
7/29	Bled 374 c.c.											
7/31	Bled 374 c.c.											
8/2	634	1,177	884	281	23.9	54	0.69	3.9	8.2	13.05	90	* Slight
8/3	Diet: 150 gm. bread, 500 c.c. milk, 1 teaspoonful ovoiderrin daily											
8/13	1,065	1,287	784	490	38.1	83	0.81	5.1	8.6	12.35	104	* Slight
8/13	Diet: 150 gm. bread, 500 c.c. milk, 2 teaspoonfuls ovoiderrin daily											
8/20	1,148	1,247	750	490	39.3	92	0.79	5.8	7.8	12.20	102	Slight
8/27	1,057	1,185	706	468	39.5	89	0.75	5.9	6.6	11.65	102	Slight
9/3	1,075	1,273	783	477	37.5	84	0.96	4.9	6.4	11.55	110	Slight
9/3	Diet: Mixed, with extra food (meat) . . . No ovoiderrin											
9/10	1,180	1,382	806	477	34.4	85	0.85	5.0	6.6	15.00	106	* Slight
9/17	1,410	1,658	1,052	588	35.5	85	0.83	5.1	6.2	15.00	110	* Slight
9/24	1,915	1,982	1,120	842	42.5	97	0.83	5.8	6.4	16.80	118	

\* Poikilocytosis of red blood cells.

Table 84 may, at first sight, be favorable to ovoiderrin as influencing the curve of blood regeneration. On careful analysis, however, we note very little, if any, change which may be attributed to the drug. Compare Table 84 with Table 92, an experiment of similar type during which sodium cacodylate was administered. There is little difference in reaction. Another experiment on this same dog is recorded (Table 86) in which a salt mixture containing a small amount of iron was given. This salt mixture seems to exert a somewhat favorable influence—a much more decided influence than the iron alone. Therefore, this minimizes the actual influence of the iron on the hemoglobin regen-

eration. The ovoferrin (Ferri vitellinum syntheticum) was obtained from the University Hospital.

Table 84 shows a sharp jump in hemoglobin, red hematocrit and pigment volume during the first ten days following the double bleeding. This is often observed after two bleedings, and has less significance than when following three bleedings, which tend to lessen this "reserve factor." We believe this reaction has little relation to the drug. During the next three weeks on the drug the pigment volume remains unchanged, although there are slight fluctuations in red hematocrit and hemoglobin. This means that the "maintenance factor" alone is being supplied. A change to a heavy mixed diet with cooked meat brings about little change in hemoglobin and hematocrit values, but the great gain in weight is associated with much increase in blood volume and actually the pigment volume gives the true picture which is a rapid increase in actual amount of formed hemoglobin in the body. The pigment volume almost doubles in this short period, associated with a gain in weight of 5 kilos. This shows again the necessity of blood volume measurement in work of this sort and shows the comparative value of iron and meat as influencing hemoglobin formation in the body under these conditions. We can attribute little value to the drug but the meat diet at once shows a striking reaction.

TABLE 85.—BLOOD REGENERATION—OVOFERRIN  
Dog 20-2. Bull mongrel. Male. Young adult

Date, 1920	Pigment Volume Hb. per Cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
7/29	2,000	C.c. 1,715	C.c. 706	C.c. 904	% 52.6	% 117	0.79	7.4	7.2	Kg. 15.15	C.c. 113	* Slight
7/29	Diet: Bread and milk											
7/30	Bled 430 c.c.											
7/31	Bled 430 c.c.											
8/ 2	898	1,261	863	392	31.1	71	1.10	3.2	6.8	14.45	87	
8/ 3	Diet: 150 gm. bread, 500 c.c. milk, 1 teaspoonful ovoferrin daily											
8/13	1,310	1,447	803	638	44.1	90	0.74	6.1	6.0	14.05	103	
8/13	Diet: 150 gm. bread, 500 c.c. milk, 2 teaspoonfuls ovoferrin daily											
8/20	1,513	1,428	786	636	44.5	106	0.88	6.0	6.8	13.75	104	* Slight
8/27	1,430	1,430	780	636	44.5	100	0.77	6.5	5.2	13.65	105	* Slight
9/ 3	1,670	1,535	774	742	48.3	109	0.72	7.6	6.0	13.55	113	* Slight
9/10	1,523	1,419	744	661	46.6	107	0.85	7.3	6.4	13.20	107	* Slight
9/17	1,665	1,445	765	668	46.3	111	0.83	6.7	5.8	13.20	109	* Slight
9/17	Diet: Mixed.† No ovoferrin											
9/24	1,838	1,795	955	822	45.8	104	0.80	6.5	6.0	16.00	112	* slight

\* Polkilocytosis of red blood cells.

† Food poor in meat.

Table 85 shows a somewhat favorable reaction following two bleedings. The anemia level in this experiment was not sufficiently reduced, and a reaction of this type would be expected on bread and milk alone. Compare this experiment with another on the same dog (Table 90) using Fowler's solution. The change in blood volume is striking when the dog is put on a liberal mixed diet and the corresponding adjustment of hemoglobin and hematocrit values is of interest.

TABLE 86.—BLOOD REGENERATION—SALT MIXTURE \*

Dog 20-3. Bull mongrel. Male. Adult

Date, 1919	Pigment Volume Hb. per cent. of Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
10/27	1,900	C.c., 1,478	C.c., 736	C.c., 721	% 48.8	% 129	0.93	6,9	8.8	Kg., 16.55	C.c., 89	
10/27	Diet: Bread and milk											
10/28	Bled 370 c.c.											
10/29	Bled 370 c.c. No distress											
10/31	778	1,045	732	303	29.0	74	0.95	3.9	22.6	15.55	67	
10/31	Bled 261 c.c.											
11/ 3	661	1,030	740	271	26.3	64	0.97	3.3	16.8	15.35	67	
11/ 3	Diet: 175 gm. bread, 2 gm. salt mixture,* 500 c.c. milk											
11/13	1,090	1,160	697	454	39.1	94	0.89	5.3	9.2	15.50	75	
11/20	1,580	1,421	765	643	45.2	111	0.76	7.3	9.0	15.30	93	+ Slight
11/26	1,548	1,421	711	697	49.0	109	0.68	8.0	8.0	14.75	96	+ Slight
12/ 3	1,545	1,400	700	686	49.0	110	0.68	8.1	6.8	14.70	95	+ Slight
12/10	1,666	1,436	718	706	49.1	116	0.68	8.5	6.8	14.35	100	+ Slight
12/17	1,445	1,343	674	656	48.8	108	0.74	7.3	7.4	14.15	95	+ Slight
12/24	1,474	1,333	666	654	49.0	110	0.65	8.4	13.6	14.00	95	+ Polk. - +

Beginning dietary deficiency disease. Recovery.

\* Salt mixture No. 185 (McCullum and Simmonds):<sup>†</sup> NaCl, 8.65 gm.; MgSO<sub>4</sub> (anhydrous), 13.50 gm.; NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O, 37.35 gm.; K<sub>2</sub>HPO<sub>4</sub>, 47.50 gm.; CaH<sub>4</sub>(PO<sub>4</sub>)<sub>2</sub>·H<sub>2</sub>O, 27.00 gm.; Fe citrate, 5.9 gm.; Ca lactate, 65.0 gm. Iron equivalent to 64 mg. or 0.96 gm. daily.

† Polkiloctyosis of red blood cells.

Tables 86, 87 and 88 show experiments which are much alike but present minor differences. This salt mixture (McCullum and Simmonds) contains per 2 gm. dose ferric citrate amounting to 64 mg. We note, in general, a somewhat more favorable reaction than is to be expected on this same diet without the salt mixture. This reaction is much like that observed on a liberal diet of rice, potatoes and milk. The regeneration during the first two weeks is quite rapid, but the return to normal is never complete, and the dogs show little change during subsequent weeks, the hemoglobin, red hematocrit and pigment volume showing minor fluctuations but remaining subnormal. It may well be debated that this favorable reaction is not to be attributed to the iron salts but to one or another of the many salts in this mixture. We

hope to make observations on the influence of various salt mixtures with and without iron, both organic and inorganic.

Two dogs developed a characteristic dietary deficiency disease after a period of several weeks. This condition will be discussed at length in a future publication.

TABLE 87.—BLOOD REGENERATION—SALT MIXTURE †  
Dog 20-1. Bull mongrel. Female. Adult

Date, 1919	Pigment Hb. per Cent. Volume Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hemato- crit	Hb.	Color Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
10/27	1,744	C.c. 1,320	C.c. 647	C.c. 668	% 50.6	% 132	0.89	7.4	12.4	Kg. 13.75	C.c. 96	
10/27	Diet: Bread and milk											
10/28	Bled 330 c.c. No distress											
10/29	Bled 330 c.c. No distress											
10/31	848	1,972	732	330	30.8	79	1.01	3.9	28.6	13.35	80	
11/1	Bled 268 c.c.											
11/1	617	984	712	253	25.7	63	1.10	2.8	22.0	13.00	76	
11/3	Diet: 200 gm. bread, 2 gm. salt mixture, † 500 c.c. milk											
11/13	898	984	596	377	38.3	91	0.80	5.7	9.6	12.50	79	
11/20	1,305	1,120	570	340	48.2	117	0.68	8.6	5.2	12.10	93	
11/22	Diet: 150 gm. bread, 2 gm. salt mixture, 500 c.c. milk											
11/26	1,386	1,255	605	638	50.8	111	0.65	8.6	5.8	11.80	106	
12/3	1,315	1,190	592	592	49.75	111	0.67	8.3	8.8	11.70	102	
12/10	1,640	1,268	690	656	51.7	129	1.02	8.3	5.6	11.25	113	
12/17	1,524	1,272	579	681	53.5	120	0.73	8.2	7.0	11.00	116	* Poik.
12/17	Diet: 200 gm. bread, 2 gm. salt mixture, 300 c.c. milk											
12/24	1,445	1,214	595	607	50.0	119	0.66	9.0	5.0	11.00	110	* Poik.
12/30	1,375	1,115	558	546	48.9	123	0.75	8.2	5.4	10.75	104	* Poik.
1/6/20	1,141	1,120	611	499	44.5	102	0.76	6.7	5.2	11.00	102	* Poik.
1/21	940	1,075	626	439	40.8	87	0.63	6.9	5.8	10.80	100	* Poik.
1/23	Diet: 250 gm. bread, 2 gm. salt mixture, 500 c.c. milk											
2/10	.....	.....	...	...	42.0	102	0.68	7.5	8.6	11.30	...	* Poik.
2/16	1,406	1,314	718	582	44.3	107	0.69	7.8	7.2	11.30	114	* Poik.

\* Poikilocytosis of red blood cells.

† Salt mixture No. 185 (McCollum and Simmonds).

Table 89 is of much interest because we have control observations on the same dog. Fowler's solution has no effect whatsoever when given daily. The curve of hemoglobin regeneration shows a very slow rise from week to week, only approaching normal after five or six weeks. The normal level is never reached during the period of twelve weeks during which Fowler's solution is administered. A transfer to a period of larger food intake without Fowler's solution shows minor

fluctuations from week to week during a period of four months. It is unusual for a dog to tolerate this limited diet for this length of time without any symptoms of dietary deficiency disease.

TABLE 88.—BLOOD REGENERATION—SALT MIXTURE \*

Dog 20-2. Bull mongrel. Male. Young adult

Date, 1919	Pigment Volume Hb. per cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
10/27	1.875	C.c. 1,496	C.c. 758	C.c. 732	% 48.9	% 125	0.79	7.9	7.0	Kg. 17.25	C.c. 87	
10/27	Diet: Bread and milk											
10/28	Bled 375 c.c.											
10/29	Bled 375 c.c. No distress											
10/31	806	1,111	700	334	30.1	78	0.93	4.2	21.6	16.35	68	
11/ 1	Bled 278 c.c.											
11/ 3	726	1,052	762	285	27.1	60	0.96	3.6	14.8	16.20	65	
11/ 3	Diet: 200 gm. bread; 500 c.c. milk, 2 gm. salt mixture*											
11/13	1,188	1,239	743	483	39.0	96	0.96	5.0	12.4	16.35	76	
11/20	1,430	1,400	788	595	42.6	102	0.80	6.4	12.2	15.75	89	+ Slight
11/22	Diet: 150 gm. bread, 500 c.c. milk, 2 gm. salt mixture*											
11/26	1,285	1,377	795	574	41.7	93	0.96	7.0	6.0	13.50	89	+ Slight
12/ 3	1,312	1,385	795	578	41.7	95	0.68	6.9	17.0	15.10	92	+ Slight
12/10	1,502	1,386	757	616	44.4	108	0.80	6.8	11.4	14.95	93	
12/16	1,252	1,318	800	505	38.3	95	0.74	6.4	6.4	14.00	94	+ Poik.†

\* Salt mixture No. 185 (McCollum and Simmonds).

† Poikilocytosis of red blood cells.

‡ Distemper and dietary deficiency disease. Recovered.

Control observations on this same dog (Table 60) show the favorable influence of a diet of cooked liver under similar conditions. Hemoglobin regeneration is complete within three weeks. This gives a striking example of the beneficial effect of certain diet factors as contrasted with certain drugs.

Table 90 shows the negative effect of Fowler's solution on the new hemoglobin regeneration. The drug is given over a period of twelve weeks. The first week shows a sharp rise which is common in such experiments. Thereafter little increase is noted from week to week. The pigment volume remains unchanged after the first three weeks. Compare other similar experiments on this same dog cited above. (Tables 85 and 88).

Following the long period of bread and milk diet, plus Fowler's solution, the dog was given a liberal mixed diet. As is not infrequent after long periods of limited diet, we note an actual fall in hemoglobin

which in this case is due to the great gain in weight and increase in plasma volume. The following two weeks show continued gain in weight, increase in plasma volume, hemoglobin and red hematocrit. This illustrates the favorable reaction, even following a prolonged limited diet period, which follows a mixed diet rich in meat.

TABLE 89.—BLOOD REGENERATION—FOWLER'S SOLUTION  
Dog 19-83. Bull mongrel. Male. Adult

Date, 1980	Pigment Volume Hb. per Cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	R. B. C. Million	W. B. C.	Weight	Blood per kilogram	Remarks
4/4	1,985	C.e. 1,470	C.e. 558	C.e. 873	% 59.4	% 135	0.61	11.8	8.2	Kg. 13.20	C.e. 111	
5/4	Diet: Bread and milk											
5/5	Bled 368 c.c.											
5/6	Bled 368 c.c.											
5/8	.....	.....	.....	.....	34.0	.....	.....	.....	.....	.....	.....	
6/8	Bled 325 c.c.											
3/10	780	1,207	850	545	28.6	64	0.77	4.2	14.2	12.75	95	* Slight
3/10	Diet: 150 gm. bread, 500 c.c. milk, 5 drops Fowler's solution											
3/17	1,114	1,475	944	516	35.0	76	0.73	5.2	12.4	12.75	116	* Slight
3/25	1,110	1,297	766	519	40.0	86	0.68	6.3	11.6	12.25	106	* Slight
4/1	1,409	1,505	828	662	44.0	94	0.65	7.2	10.4	12.00	125	* Slight
4/7	1,450	1,470	765	692	47.0	99	0.61	8.1	6.2	12.06	122	* Slight
4/15	1,485	1,470	771	685	46.6	101	0.63	7.9	6.4	11.96	123	* Slight
4/22	1,510	1,398	692	692	49.5	108	0.66	8.3	5.6	11.60	120	* Slight
4/29	1,505	1,468	745	708	48.2	102	0.59	8.7	4.8	11.55	127	* Slight
5/6	1,345	1,345	700	632	47.0	100	0.60	8.3	5.2	11.55	116	* Poik.
5/14	1,340	1,390	721	657	47.2	96	0.61	7.9	6.4	11.00	126	* Poik. +
5/21	1,294	1,276	657	606	47.5	94	0.61	7.7	6.0	10.85	117	* Slight
5/28	1,419	1,375	702	667	48.5	103	0.61	8.5	5.2	10.70	128	* Slight
5/29	Diet: 250 gm. bread, 500 c.c. milk. Fowler's solution discontinued											
6/4	.....	.....	.....	.....	44.8	102	.....	.....	.....	.....	.....	
6/11	1,305	1,393	743	587	43.7	93	0.57	8.2	6.4	11.70	114	* Slight
6/18	1,397	1,339	749	571	42.9	98	0.55	8.9	5.4	11.80	113	* Poik.
6/26	1,508	1,445	778	651	45.2	104	0.56	9.3	6.8	12.25	118	* Poik.
7/9	1,325	1,398	803	551	40.3	97	0.64	7.6	7.2	12.05	113	* Poik.
7/28	1,692	1,540	775	710	47.4	108	0.72	7.8	6.4	12.40	121	* Slight
8/18	1,960	1,621	803	803	49.5	121	0.79	7.6	6.0	12.85	126	* Poik.
8/30	1,705	1,505	780	711	47.2	113	0.74	7.6	5.8	12.10	124	* Poik.
9/8	1,630	1,538	854	669	43.5	106	0.68	7.8	6.2	12.60	122	* Poik.
9/22	1,550	1,550	894	640	41.3	100	0.69	7.2	7.2	12.75	121	* Poik.

\* Poikilocytosis of red blood cells.

Table 91 shows that another arsenical, sodium cacodylate, is inert under these conditions. The curve of blood regeneration rises slowly and uniformly during 11 weeks but never returns to normal. This reaction is typical of many recorded for bread and milk alone. A change of diet gives a prompt increase in all hemoglobin figures and the normal level is reached in three weeks. Under such conditions this reaction to meat may not be as prompt, but it illustrates this favorable

reaction in contrast to the negative influence of this drug, sodium cacodylate.

TABLE 90.—BLOOD REGENERATION—FOWLER'S SOLUTION  
Dog 20-2. Bull mongrel. Male. Young adult

Date, 1920	Pigment Volume Hb. per Cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematoerit	Hb.	Color Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
3 4	2,282	C.c. 1,915	C.c. 882	C.c. 1,913	% 52.9	% 119	0.60	10.0	13.4	Kg. 17.95	C.c. 108	
3 4	Diet: Bread and milk											
3 5	Bled 480 c.c.											
3 6	Bled 480 c.c.											
3 8	.....	.....	.....	.....	28.6	....	....	....	....	....	....	
3 8	Bled 350 c.c.											
3 10	662	1,350	1,047	289	21.4	49	0.84	2.9	33.4	17.00	9	
3 10	Diet: 150 gm. bread, 500 c.c. milk, 2 drops of Fowler's solution											
3/17	1,180	1,370	803	554	40.5	86	0.81	5.3	7.0	15.85	86	
3 18	Diet: 150 gm. bread, 500 c.c. milk, 5 drops of Fowler's solution											
3/25	1,243	1,495	904	575	38.5	83	0.78	5.3	6.8	15.60	96	
4 1	1,410	1,535	857	695	45.3	92	0.71	6.5	7.2	15.00	102	
4/ 7	1,690	1,680	885	785	46.8	99	0.73	6.8	5.4	15.05	112	
4/15	1,730	1,730	912	815	47.1	101	0.73	6.9	3.6	15.05	115	
4 22	1,715	1,715	850	850	49.5	109	0.60	8.4	6.6	14.85	115	
4/29	1,695	1,740	916	808	46.4	97	0.65	7.5	7.0	14.65	119	* Slight
5/ 6	1,530	1,570	829	734	46.5	98	0.60	8.1	6.8	14.55	108	* Polk. +
5 14	1,565	1,565	820	738	47.1	100	0.63	8.0	5.6	13.75	114	* Polk.
5 21	1,387	1,547	857	675	43.6	90	0.62	7.2	6.4	13.50	115	* Polk.
5 28	1,554	1,563	828	719	46.0	99	0.70	7.1	6.8	13.45	116	* Slight
5 28	Diet: 100 gm. bread, 300 gm. meat scraps, 500 c.c. milk. Fowler's solution discontinued											
6 4	.....	.....	....	..	43.9	99	....	....	....	....	....	
6/11	1,395	1,545	875	680	44.0	90	0.57	7.9	6.6	15.75	98	Polk.
6 11	Diet: 100 gm. bread, 450 gm. meat scraps, 500 c.c. milk											
6 18	2,148	1,865	924	924	49.5	115	0.66	8.4	10.0	16.40	114	
6/25	2,008	1,820	920	884	48.5	110	0.69	8.0	8.8	17.25	106	

\* Polkilocytosis of red blood cells.

Table 92 confirms the reaction noted in the preceding Table 91. We believe there is not a bit of evidence that the sodium cacodylate has any effect upon this reaction. There is every reason to believe that an identical reaction would have been observed in this experiment had the drug not been given. Compare Table 86 above, in which a more favorable reaction is associated with the oral administration of a standard salt mixture (McCollum and Simmonds).

#### SUMMARY

Iron in the form of Bland's pills is inert when given under controlled conditions in anemia periods under the conditions of these experiments (Paper V of this series \*).



The anemia is produced by hemorrhage, and the curve of regeneration followed week by week, the dogs being maintained on a fixed diet.

Iron in the form of ferric citrate (subcutaneously) and ovoferrin (orally) has no significant effect on the curve of hemoglobin regeneration under controlled conditions.

TABLE 91.—BLOOD REGENERATION—SODIUM CACODYLATE  
Dog 20-5. Bull mongrel. Male. Young adult

Date, 1920	Pigment Volume Hb. per Cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematocrit	Hb.	Color Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
	C.e.	C.e.	C.e.	C.e.	%	%				Kg.	C.e.	
3 4	2,340	1,800	774	1,008	56.0	131	0.75	8.7	12.2	13.75	131	
3 4	Diet: Bread and milk											
3/ 5	Bled 450 c.c.											
5/ 6	Bled 450 c.c.											
3/ 8	.....	.....	...	...	27.5	...	...	...	.....	.....	...	
3/ 8	Bled 300 c.c.											
3/10	520	1,170	924	234	20.0	44	0.77	2.9	13.6	13.40	87	
3/10	Diet: 150 gm. bread, 500 c.c. milk, 0.1 gm. sodium cacodylate subcutaneously											
3/17	637	1,250	946	310	24.8	51	0.77	3.3	12.6	13.25	94	
3/25	798	1,310	927	369	28.2	61	0.65	4.7	11.8	13.00	101	Slight
4 1	782	1,325	922	392	29.6	59	0.54	5.5	11.2	12.90	103	* Poik. +
4/ 7	1,079	1,370	872	512	37.3	79	0.50	7.8	8.8	12.85	107	* Poik.
4/15	970	1,320	857	448	34.0	73	0.52	7.1	8.4	12.85	103	* Poik. ++
4/22	1,162	1,352	863	542	40.1	86	0.45	9.6	7.6	12.45	108	* Poik. ++
4/29	1,125	1,380	823	548	39.7	81	0.60	7.6	8.8	12.55	110	* Poik.
5 6	1,258	1,435	840	600	41.2	86	0.49	8.9	8.2	12.40	117	* Poik. ++
5/14	1,232	1,360	754	592	43.6	92	0.58	8.0	6.0	12.25	111	* Poik. ++
5/21	1,225	1,385	788	584	42.2	88	0.50	8.9	6.2	12.40	112	* Poik. ++
5/28	1,330	1,420	778	634	44.7	94	0.73	9.4	5.0	12.25	116	* Poik. +
5 28	Diet: 100 gm. bread, 300 gm. meat scraps; 500 c.c. milk. Sod. cacodylate discontinued											
6 4	.....	.....	...	...	45.0	100	.....	...	.....	.....	...	
6 11	1,745	1,630	808	768	46.5	106	0.58	9.1	6.0	14.10	117	* Poik
6 11	Diet: 100 gm. bread, 450 gm. meat scraps, 500 c.c. milk											
6/18	1,998	1,745	876	852	48.8	114	0.58	9.8	17.4	14.00	117	
6/25	2,355	1,861	830	906	53.5	125	0.63	10.5	16.4	15.50	120	

Poikilocytosis of red blood cells.

Iron forming a part of a standard salt mixture (McCullum and Simmonds) may be concerned in a somewhat favorable anemia reaction, but even this reaction is not surely related to the iron salt. At best this reaction does not compare favorably with those recorded in association with certain potent diet factors.

Iron in the form of hemoglobin (organic iron) may be concerned in the somewhat favorable reaction observed following the administration of hemoglobin orally, intraperitoneally or intravenously. But the iron may be less concerned in this reaction than the pyrrol complex (Paper V of this series <sup>4</sup>).

Arsenic in the form of sodium cacodylate or Fowler's solution is inert in these same anemia periods. No drug has been tested which can compare with the meat factors in stimulating a rapid regeneration of hemoglobin during these anemia periods induced by simple hemorrhage.

TABLE 92.—BLOOD REGENERATION—SODIUM CACODYLATE  
Dog 20-3, Bull mongrel, Male, Young adult

Date, 1920	Pigment Volume Hb. per Cent. Times Blood Volume	Blood Volume	Plasma Volume	R. B. C. Volume	R. B. C. Hematoerith	Hb.	Color Index	R. B. C., Million	W. B. C.	Weight	Blood per Kilogram	Remarks
3/ 4	2,165	C.c. 1,865	C.c. 838	C.c. 1,010	% 54.2	% 116	0.60	8.4	13.2	Kg. 16.95	C.c. 110	
3/ 4	Diet: Bread and milk											
3/ 5	Bled 467 c.c.											
3/ 6	Bled 467 c.c.											
3/ 8	.....	.....	...	...	24.4	...	....	...	....	.....	...	
3/ 8	Bled 200 c.c.											
3/10	640	1,320	1,009	294	22.3	49	0.93	2.6	30.8	16.40	80	
3/10	Diet: 150 gm. bread, 500 c.c. milk, 0.1 gm. sodium cacodylate subcutaneously											
3/17	1,180	1,548	1,018	508	32.8	79	0.81	4.3	10.6	16.05	96	
3/25	1,297	1,563	923	633	40.5	83	0.78	5.3	9.4	15.00	104	* Slight
4/ 1	1,480	1,625	896	745	45.8	91	0.72	6.3	9.6	15.00	108	* Slight
4/ 7	1,580	1,692	850	726	45.3	99	0.81	6.1	8.2	14.85	108	* Slight
4/15	1,755	1,675	874	796	47.5	105	0.81	6.5	7.8	14.20	118	* Slight
4/22	1,775	1,715	864	840	49.0	103	0.71	7.3	5.6	14.25	120	* Slight
4/29	1,788	1,700	808	876	51.5	105	0.65	8.1	6.8	13.96	122	* Slight
5/ 6	1,815	1,700	904	834	47.4	103	0.72	7.2	6.4	13.80	127	* Poik.
5/14	1,690	1,497	752	732	48.9	113	0.86	6.6	10.6	13.35	112	* Slight
5/21	1,317	1,480	829	636	43.0	89	0.74	6.0	9.4	13.05	113	* Poik.
5/28	1,310	1,455	837	612	42.0	90	0.76	5.9	8.4	12.55	116	* Slight
5/29	Diet: 100 gm. bread, 300 gm. meat scraps, 500 c.c. milk. No sodium cacodylate											
6/ 4	.....	.....	...	...	43.6	101	....	...	....	.....	...	
6/11	1,607	1,630	848	765	47.0	99	0.70	7.0	7.2	14.20	114	
6/11	Diet: 100 gm. bread, 450 gm. meat scraps, 500 c.c. milk											
6/18	1,852	1,637	836	816	49.2	112	0.67	8.4	12.4	14.65	113	
6/25	1,782	1,647	851	784	47.6	108	0.68	7.9	10.6	13.75	105	

\* Poikilocytosis of red blood cells.

These carefully controlled experiments give no support to the time honored custom of administering iron and certain other drugs in conditions of simple anemia. The burden of proof now rests with those who claim that any given drug is potent under such conditions. In such experiments or clinical observations the diet factors must be carefully studied. We believe it will be of much clinical importance to record accurate observations in human cases, giving particular attention to a variety of diet factors.

## THE CREATININ COEFFICIENT IN PULMONARY TUBERCULOSIS \*

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In the light of the significant rôle of creatinin excretion in endogenous metabolism, it was deemed that it might prove of some interest to determine the creatinin coefficient in a series of graded, clinically uncomplicated, cases of pulmonary tuberculosis, particularly as there are operative, in this condition, two somewhat opposing factors of undoubted metabolic importance, namely continued pyrexia and progressive wasting of muscle mass.

But few cases of pulmonary tuberculosis have been reported in the literature from this point of view, and these show findings both indeterminate and in poor accord. Thus Hofmann,<sup>1</sup> employing a now obsolete procedure of creatinin determination and making no provision as to diet control, reports one advanced, though apparently afebrile case (patient aged 34), in which there was noted a slight decrease of creatinin output—0.496 gm. per twenty-four hours as opposed to his normal value of 0.687 gm. Van Hoogenhyze and Verploegh,<sup>2</sup> on the basis of Folin's technic, and utilizing a low protein diet, report a febrile case (patient aged 72) marked by slight decrease in creatinin excretion—1.05 gm. (average) per twenty-four hours. McClure,<sup>3</sup> also utilizing Folin's technic and employing a modified (purin and nuclein free) Shaffer-Coleman<sup>4</sup> diet, reports four febrile cases. The first case (patient aged 19), in which there was a positive Wassermann reaction, showed irregular increase with wide range (from 0.606 to 2.052 gm. per twenty-four hours). In the second case (patient aged 27), complicated by hemopneumothorax, there was likewise noted occasional increase in creatinin output with a range of from 0.624 to 1.956 gm. per twenty-four hours. In the third case, one of tuberculous bronchopneumonia (patient aged 28), there was observed practically no increase and a range of from 0.607 to 1.291 gm. per twenty-four hours, while, in the last case (patient aged 25), also one of tuberculous bronchopneumonia, there was found a slight decrease, with a range of from 0.540 to 1.000 gm. per twenty-four hours.

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\* From the laboratory of the Sea View Hospital.

1. Hofmann, K. B.: *Virchows Arch. f. path. Anat.* **48**:358, 1869.

2. Van Hoogenhyze, C. J. C., and Verploegh, H.: *Ztschr. f. Physiol. Chem.* **57**:162, 1908.

3. McClure, C. W.: *Arch. Int. Med.* **22**:719 (Dec.) 1918.

4. Shaffer, P. A., and Coleman, W.: *Arch. Int. Med.* **4**:538 (Nov.) 190

In regard to the normal rate of creatinin excretion, it has been determined by Shaffer<sup>5</sup> that the creatinin coefficient (milligrams of creatinin-nitrogen excreted per kilogram of body weight in twenty-four hours) represents a practical constant in ordinary individuals, the average figure being 8.1. Values under 7, he found, are distinctly abnormal, except in aged, poorly developed, or obese subjects. This constant seems to be the most convenient and generally accepted medium for the expression of creatinin values.

#### PROCEDURE

Three groups of five cases of pulmonary tuberculosis, uncomplicated as far as could be determined clinically, were selected in accordance with Rathbun's<sup>6</sup> classification, as representing three progressive grades of disease activity. Organically, these cases were all of his "moderately advanced" or "far advanced" (third group) types (q. v.), falling functionally or symptomatically, however, into the three groups of his classification, as follows: A, afebrile, absence of constitutional disturbance, ambulant and doing light work; B, slightly febrile, slight constitutional disturbance, in bed one-half day; C, definitely febrile, marked constitutional disturbance, confined to bed entire day and general condition serious to critical. The cases were all males and care was taken to select no patients showing evidence of obesity and to exclude adolescent and senile types.

The subjects were placed on a strictly meat free diet, and after a preliminary period of forty-eight hours, creatinin determinations were made on three successive days from preserved twenty-four-hour urine samples. These determinations were made according to Folin's method, as outlined by Hawk,<sup>7</sup> utilizing the Duboscq colorimeter and a potassium bichromate standard, the average of triplicate readings being taken in each case. Calculations were made on the basis of milligrams of creatinin-nitrogen per kilogram of body weight excreted per twenty-four hours (Shaffer's creatinin coefficient) and the results tabulated as shown in the accompanying table.

#### COMMENT

It will be seen that the findings have been, for the most part, of consistent uniformity, with most variation in group A, and that, in all three groups, the average values have been definitely below the normal constant (8.1), as determined by Shaffer. On the other hand, there seems to be but little difference between the three grades, as compared

5. Shaffer, P.: *Am. J. Physiol.* **23**:1, 1908.

6. Rathbun, W. L.: *Tuberculosis*, Monograph, Dept. Health, New York City No. 4, March, 1917.

7. Hawk, P. B.: *Physiologic Chemistry*, Philadelphia, Ed. 6, 1918.

CREATININ COEFFICIENT OF FIVE SUBJECTS ON A MEAT-FREE DIET

Case	Grade	Date	Creat- Inn Coeff- cient	Body Weight, Kg.	Age	Case	Grade	Date	Creat- Inn Coeff- cient	Body Weight, Kg.	Age	Case	Grade	Date	Creat- Inn Coeff- cient	Body Weight, Kg.	Age
1 Ra.	A	7/30/20	6.07	66.1	29	G P.	B	8/3/20	7.14	48.7	30	11-Re.	C	7/28/20	6.88	52.7	30
		7/31/20	5.38					8/4/20	8.22					7/29/20	6.37		
		8/1/20	4.88					8/5/20	6.34					7/30/20	7.59		
		Average	5.44					Average	7.26					Average	6.94		
2 Wy.	A	7/30/20	....	74.0	36	7-W.W	B	8/3/20	7.05	48.9	54	12-M.	C	7/28/20	5.53	51.3	34
		7/31/20	7.56					8/4/20	6.56					7/29/20	5.58		
		8/1/20	5.34					8/5/20	7.68					7/30/20	....		
		Average	6.46					Average	7.09					Average	5.55		
3 D.	A	7/30/20	7.04	64.3	61	8 Ko.	B	8/3/20	6.65	57.7	36	13-B.	C	7/28/20	3.82	56.8	28
		7/31/20	....					8/4/20	6.26					7/29/20	4.07		
		8/1/20	....					8/5/20	6.37					7/30/20	5.56		
		Average	7.04					Average	6.22					Average	4.48		
4 H.	A	7/30/20	5.55	71.3	29	9 By.	B	8/3/20	5.38	52.2	24	14-G.	C	7/28/20	6.18	46.3	30
		7/31/20	4.93					8/4/20	7.29					7/29/20	5.82		
		8/1/20	1.16					8/5/20	....					7/30/20	6.27		
		Average	1.88					Average	6.33					Average	6.09		
5 Kr.	A	10/14/20	3.06	64.5	51	16-T.W.	B	8/3/20	7.24	62.7	40	15-L.	C	7/28/20	....	50.3	39
		10/15/20	3.58					8/4/20	7.04					7/29/20	3.38		
		10/16/20	4.47					8/5/20	7.11					7/30/20	6.91		
		Average	3.70					Average	7.13					Average	6.14		
General average.....			5.50	65.4		General average.....			6.80	54.0		General average.....			5.84	51.4	

with one another, save that the B cases appear, on the whole, to show a slightly higher coefficient than either A or C. This might possibly be accounted for on the basis of the increased catabolism, due to fever and increased disease activity, not present in A, and not offset, as in C, by extreme wasting and general debility and asthenia. It would seem therefore, that in pulmonary tuberculosis, creatinin excretion increases with increase in disease activity, up to a certain point, at which a decrease becomes manifest dependent, probably, on progressive tissue wasting and generally lowered plane of vital activity.

These findings bear out, in a general way, the tendency indicated in the work of Hofmann and Van Hoogenhyze and Verploegh and, also, may serve to throw some light on the apparent disagreement between their findings and those of McClure.

It is of interest to note, in this connection, that McCann and Barr,<sup>8</sup> working with tuberculous patients from the point of view of calorimetric investigation, have recently found that due to weight-loss compensating for increase in metabolism dependent on disease activity, the basal heat production, in this disease, may represent a value definitely below that obtaining in health for the same individual.

#### SUMMARY

On the basis of the data secured in this study, it seems that, in apparently clinically uncomplicated cases of pulmonary tuberculosis, the creatinin coefficient is slightly below the average normal figure, and that it reaches its greatest height in middle grade cases, i.e., those in which increased catabolism, due to disease activity, has not yet been offset by excessive tissue waste and generally lowered vitality.

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8. McCann, W. S., and Barr, D. P.: *Arch. Int. Med.* **26**:663 (Dec.) 1920.

## REMARKS ON STANDARDS FOR NORMAL BASAL METABOLISM.\*

J. H. MEANS, M.D., AND M. N. WOODWELL, A.B.

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Indirect calorimetry, as a result of the pioneer work of DuBois and his collaborators,<sup>1</sup> has become generally adopted in the last two or three years, in this country at least, as a routine method of laboratory diagnosis in certain diseases, especially in those of the ductless glands. As a functional test of the thyroid gland, the level of the basal metabolism is being determined at the present time in many clinics.

Clinicians, of course, wish to use the most accurate criteria available in judging of the normality or abnormality of the basal metabolism of their patients, and yet at present they may well be puzzled in choosing between the several methods that have been proposed for the purpose by various investigators. It is with the hope of throwing light on this phase of the subject that the present communication is made.

### METHODS FOR PREDICTING THE BASAL METABOLISM OF NORMAL PERSONS

*Body Surface Law.*—The search for suitable criteria has centered chiefly about the so-called body surface law of Rubner. The principle embodied in this law, which is that the basal metabolism is a simple function of the body surface, has been disputed by Benedict,<sup>2</sup> and quite lately by Dreyer,<sup>3</sup> and as Boothby and Sandiford<sup>4</sup> have recently pointed out, such objections, in a strict sense, are valid. Nevertheless, in a broader sense Rubner's Law has never been disproved, and while it may be true that the basal metabolism is not strictly proportional to, nor, perhaps, determined by, surface area, the fact remains that it is more nearly proportional to area than to any other one factor so far discovered. Pertinent in this connection are the studies by Means,<sup>5</sup> of obesity,<sup>6</sup> which showed that even in very marked grades of obesity, there was no fundamental deviation from normal in basal metabolism

\* From the Medical Service of the Massachusetts General Hospital, aided in part by a gift from Dr. William Norton Bullard.

1. Du Bois, E. F., et al.: Series of papers on Clinical Calorimetry beginning, *Arch. Int. Med.* **15**:793 (July) 1915.

2. Benedict, F. G.: *Boston M. & S. J.* **182**:243, 1915.

3. Dreyer, G.: *Lancet* **1**:289, 1920.

4. Boothby, W. M., and Sandiford, I.: *Basal Metabolic Rate Determinations*, Philadelphia, W. B. Saunders Co., 1920.

5. Means, J. H.: *Proc. Soc. Exper. Biol. & Med.* **12**:13, 1914; *J. M. Research* **32**:121, 1915; *Arch. Int. Med.* **17**:704 (July) 1916.

6. The data on these cases of obesity together with that on one new one is given in Table 2 of the present paper.

expressed in terms of surface area, whereas there was a marked reduction (30 per cent. or more) when it was expressed in terms of body weight.

The history of the body surface law is very completely covered in the recent monograph of Harris and Benedict.<sup>7</sup> The difficulty which has confronted investigators since the time when the relationship between metabolism and area was first appreciated has lain chiefly in the lack of an accurate method for measuring or calculating body surface area from the body weight, such for example as those of Meeh,<sup>8</sup> and of Lissauer.<sup>9</sup> For persons of normal build they may serve very well, but for those who vary from the normal, they may serve badly. Of two persons of the same weight, one being short and stout, the other tall and thin, the latter would have the greater actual area, yet by Meeh's or similar formulas the calculated area would be the same.

*Du Bois Linear Formula.*—It was to overcome just such faults in formulas of the Meeh type that the Du Bois formulas were devised. By the first of these, the so-called linear formula,<sup>10</sup> which was first published in 1914, the body surface is calculated from about nineteen measurements of the body. The principle is to divide the body into parts and calculate the area of each part from its length multiplied by its average circumference and by a constant. The sum of the parts gives the total body surface area. The constants for the several parts were derived from the areas of the parts as determined by actual casts. Casts were made of the bodies of ten individuals of widely different shapes.<sup>11</sup> It was found that the area as calculated by the linear formula varied on an average less than 1.7 per cent. from the areas as actually measured from the casts. It was with the advent of this formula that calorimetry became available to the clinician.<sup>12</sup> In the linear formula, the clinical investigator is equipped with a method that will give him accurately the surface area of individuals of any shape.

*Du Bois Height Weight Formula and Chart.*—In 1916, the Du Boises<sup>14</sup> brought out a still simpler formula, the so-called height-weight

7. Harris, J. A., and Benedict, F. G.: Carnegie Institution of Washington, Publication No. 279, 1919.

8. Meeh: *Ztschr. f. Biol.* **15**:425, 1879.

9. Lissauer: *Jahrb. f. Kinderh., N. F.* **58**:392, 1903.

10. Du Bois, D., and Du Bois, E. F.: *Proc. Soc. Exper. Biol. & Med.* **12**: 16, 1914. *Ibid.*, *Arch. Int. Med.* **15**:868 (July) 1915.

11. The cast of one of these, Mrs. McK. (Table 2), was made at the Massachusetts General Hospital.

12. In addition to the obesity data given in Table 2, attention is called to a previous paper by one of us (J. H. M.<sup>13</sup>), in which it was shown that even in normal persons there was less variation in the metabolism by the linear formula, than by that of Meeh.

13. Means, J. H.: *J. Biol. Chem.* **21**:263, 1915.

14. Du Bois, D., and Du Bois, E. F.: *Arch. Int. Med.* **17**:863 (July) 1916.



formula. This was worked out from the results obtained in a large series of persons by the linear formula, and enables one to obtain the surface area directly from the height and weight.<sup>15</sup>

The height-weight formula, which has been still further simplified into the height-weight chart, is the method in use in most clinics today. At the Massachusetts General Hospital the determination of the basal metabolism in disease was begun early in 1914, from then until the fall of 1915 the linear formula was used; since then the height-weight chart has been used, except that in very stout persons we still use the linear. In this clinic as in other clinics the calories per square meter per hour are compared with the Sage Institute normal standards. These standards have been changed slightly from time to time; the most recent ones will be found in the paper of Aub and Du Bois<sup>16</sup> published in 1917.

*Harris-Benedict Prediction Tables.*—As has been said, clinical calorimetry has become part of the diagnostic armamentarium of many clinics. It is, therefore, obviously desirable that in so far as possible uniform standards be employed. As has been indicated, the Du Bois height-weight chart with the Sage Institute standards is the method in common use today. However, since no lesser authorities than Benedict<sup>7</sup> in this country and Dreyer<sup>3</sup> in England have each recently proposed new methods for predicting normal metabolism, the clinical calorimetrist may well be in doubt as to which of these, the Du Bois, the Harris-Benedict, or the Dreyer, he should use.

TABLE 1.—COMPARISON OF PREDICTION METHODS. DATA ON NORMAL PERSONS

	Average Deviation Without Regard to Sign, per Cent.			Average Deviation With Regard to Sign, per Cent.		
	Du Bois Height- Weight Formula	Dreyer	Harris- Benedict	Du Bois Height- Weight Formula	Dreyer	Harris- Benedict
Series of 8 normal men						
Means <sup>15</sup> .....	6.21*	3.70	4.40	-6.21*	-2.12	-4.40
Series of 31 normal men						
Carpenter et al. <sup>2</sup> .....	5.10*	5.94	5.30	-1.63*	-0.10	+0.45

\* Our calculations; other figures are from Dreyer's paper.<sup>2</sup>

The Harris-Benedict method takes the form of a series of tables in which are given prediction figures of what the metabolism should be in a normal adult of either sex and of any height, weight or age. The figures were developed from the data of observations made on 103 women and 136 men at the Carnegie Nutrition Laboratory in Boston.

15. For the mathematical expression one is referred to the original paper.

16. Aub, J. C., and Du Bois, E. F.: Arch. Int. Med. **19**:823 (July) 1917.

*The Dreyer Formulas.*—The Dreyer formulas are several. They take into consideration one less factor than either the Du Bois or the Harris-Benedict. The last two take into consideration height, weight, age and sex. The Dreyer formulas are based on age, sex, and one other factor, either weight, trunk length or circumference of thorax. Dreyer derived his constants from the Harris-Benedict data.

*Comparison of the Du Bois, Harris-Benedict and Dreyer Methods.*—The immediate object of this paper is to scrutinize these three methods, the Du Bois height-weight formula or chart used in conjunction with the Sage standards, the Harris-Benedict prediction tables, and the Dreyer weight formula. An attempt will be made to learn their respective merits and limitations, their similarities and dissimilarities.

We have several ways of making such a scrutiny. In the first place, we can see which method actually predicts with the least error the metabolism of healthy persons of normal build. Next, we can do the same with persons with abnormally shaped bodies, obese subjects for example. Lastly, we can compare the deviations from normal by the several methods (one with another) in patients whose metabolism is known to be abnormal.

*In Normal Persons.*—There are shown in Table 1 the average variations by these methods of a series of eight normal men studied by Means<sup>13</sup> and of a series of thirty-one studied by Carpenter and collaborators.<sup>7</sup> The results obtained in both these series by the Harris-Benedict method have been discussed by Harris and Benedict,<sup>7</sup> and those obtained by both Harris-Benedict and Dreyer methods have been discussed by Dreyer.<sup>2</sup>

In analyzing such a series of results, we have two modes of attack. We can compare the average deviations from different standards or predictions, regardless of whether they are too high or too low, that is to say, without regard to sign, or we can cancel the positive deviations against the negative and find the average deviation with regard to sign. The former way gives the truest idea of the success in metabolism prediction of the method under consideration, for the lower the average deviation without regard to sign the closer has the predicted come to the observed in the majority of instances. This is particularly true if in addition to the average, we know the maximum deviation of the series.

The average deviation with regard to sign, that is to say, when plus deviations neutralize minus ones of the same magnitude, tells us chiefly whether the series has a positive or negative bias or trend, but we must regard not only this average but at the same time the distribution of its individual components about it, the probability curve

in other words, lest we be led astray by the cancellation of several small plus deviations by a single large minus one, or vice versa.

A case in point is the characterization by Harris and Benedict as of an anomalous nature the Means series of eight normal men as well as the series of ten normal men of Magnus-Levy and Falk.<sup>17</sup> The interpretation here is dependent upon the significance given to averages. All of the members of the Means series deviate below the predicted metabolism level while seven out of ten of the Magnus-Levy and Falk series deviate above it. This, we are prepared to admit, may mean that the former series is composed of very slightly subnormal individuals and the latter of very slightly supernormal ones. We cannot, however, agree with Harris and Benedict that the members of either of these series are more abnormal than are those of the Carpenter series merely because in the Carpenter series the positive deviations counterbalance the negative. There are five individuals in the Carpenter series, or nearly one-sixth of the whole, all of whom are more abnormal than are any of those in the Means series. The fact that some are supernormal and some subnormal does not increase the normality of the series as a whole. The average deviation without regard to sign is the true index of the normality or lack of normality of a series. That factor is less (4.40 per cent.) in the case of the Means series than in that of the Carpenter series (5.30 per cent.). We cannot, therefore, agree that either the Means series or the Magnus-Levy and Falk series are anomalous, or that they are unfit for combination with other series for purposes of generalization. The low average deviation in the Means series shows a high grade of normality in that series. The fact that the deviations, though slight, were all in the direction of subnormality may be explained by the fact that this series was entirely composed of subjects of a non-athletic type, whereas the prediction figures were based on subjects of all types.

With these remarks as to the significance or lack of significance of averages, let us now turn to Table 1 and note the results obtained by the three different formulas. In the case of the Means series the lowest average deviation was obtained with the Dreyer formula, in that of the Carpenter series it was with the Du Bois formula. In both series the lowest deviation with regard to sign was with the Dreyer formula. That is to say, with the last named there is the least tendency toward a positive or negative trend. The greatest average deviations were with the Du Bois formula in the case of the Means series, and with the Dreyer in the case of the Carpenter series. In other words, as applied to two series of normal men the three methods give deviations of about the same order of magnitude.

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17. Magnus-Levy, A., and Falk: *Arch. f. Anat. u. Physiol. Suppl.*, 1899, p. 314.

*In Obese Persons.*—Let us now apply these formulas to persons of abnormal build. In Table 2 are given the data on the five cases of obesity previously published by Means<sup>5</sup> together with those of one new case, Mrs. F. When originally published, the metabolism of these patients was calculated in terms of the linear formula only. We have now added the height-weight, Harris-Benedict and Dreyer data. The conclusion was drawn originally that there was no fundamental change in the metabolism in obesity. As will be seen in Table 2, the results obtained with the other methods are in general similar to those obtained with the linear formula. The closest prediction is that of the Harris-Benedict method, the average deviation being only 3.3 per cent., the linear comes next with 4.9 per cent., then the height-weight formula with 5.6 per cent., and lastly, the Dreyer with 6.5 per cent. Taking signs into consideration, we find a plus bias for the series with the height-weight and Dreyer formulas and a negative one with the Harris-Benedict and linear. The maximum deviation for all six subjects by all four methods is only +11.5 per cent. in the case of Mrs. B. by the height-weight formula. By the linear she is -1.7 per cent., and by the Harris-Benedict +1.7 per cent. and by the Dreyer +10.5 per cent. Mrs. McK. is slightly subnormal by all methods, Mrs. McL. is slightly supernormal by all methods, and the rest show deviations above by some and below by other of the methods. Taken as a whole, we believe these figures constitute strong confirmation of the conclusion originally drawn from the linear results alone, namely, that there is no fundamental change in the level of the basal metabolism in simple obesity. They all show that in obesity the Harris-Benedict method gives a slightly closer prediction than the Du Bois formulas, and they closer than the Dreyer. The last is not surprising since the latter method takes no account of height. In fact, the extraordinary thing is that the Dreyer prediction is as good as it is.

*In Persons with Abnormal Metabolism.*—So much for the relative merits of these three methods of prediction in the case of persons who may be expected a priori to have normal metabolism. Let us now apply them to persons who may be expected to have abnormal metabolism. The problem here is a slightly different one. It is not so much a question of finding the method which in the case of abnormal metabolism gives the least deviation from normal, as it is of comparing the general trend of the deviation by one method, with that by another, to see, in other words, whether in a series of patients with varying elevations or depressions of metabolism the deviations by one method run parallel with those by another, or whether there is any constant tendency for one method to give greater deviations than another.

To accomplish this purpose, we have prepared three figures in which we have plotted the deviations shown by a series of 160 hospital patients.

We used the graphic method in this instance, believing that it would more simply demonstrate the facts than would tables of numbers. The patients, data on whom constitute the series, were selected only with a view to getting the greatest possible range of deviation. As a result, we have chiefly patients with myxedema with subnormal metabolism, and patients with toxic goiters with supernormal metabolism, together with a few patients with essentially normal metabolism.

TABLE 2.—COMPARISON OF PREDICTION METHODS. DATA ON OBESE PERSONS

Subject	Age, Years	Height, Cm.	Weight, Kg.	Total Calories per Hour						Per Cent. Deviation Observed From Predicted			
				Predicted									
				Observed	Du Bois Height-Weight Formula	Du Bois Linear Formula	Harris-Benedict	Dreyer	Du Bois Height-Weight Formula	Du Bois Linear Formula	Harris-Benedict	Dreyer	
Mrs. B. ....	44	163.0	179.0	104.4	94.3	106.2	102.6	94.5	+11.5	-1.7	+1.7	+10.5	
Mrs. McK. ....	48	144.5	103.0	64.7	68.4	70.6	70.1	70.8	-5.3	-8.4	-7.7	-8.7	
Mrs. L. L. ....	36	163.5	142.6	91.0	86.9	100.7	89.7	86.6	+4.7	-9.6	+1.4	+5.1	
Mrs. McL. ....	46	157.5	127.0	84.2	79.6	82.4	81.1	79.1	+5.8	+2.2	+3.9	+6.5	
Mrs. Sha. ....	30	155.0	110.2	75.3	74.8	79.6	77.3	78.0	+0.8	-5.2	-2.6	-3.4	
Mrs. F. ....	63	165.0	141.0	88.0	83.3	90.3	85.9	81.8	+5.6	-2.6	+2.4	+5.1	
Average deviation without regard to sign.....									5.6	4.9	3.3	6.5	
Average deviation with regard to sign.....									+3.8	-4.2	-0.1	+2.5	

In Figure 1 are compared the deviations by the Du Bois height-weight chart method, with those by Harris-Benedict. A glance at this will show that the two methods give essentially parallel results. The Harris-Benedict deviations are generally a few points higher than the Du Bois ones. A similar comparison has already been made by Boothby and Sandiford,<sup>4</sup> and we were gratified to find that our own results are very nearly identical to theirs. For example, Boothby and Sandiford found the average deviation 6.5 points higher by Harris-Benedict than by Du Bois, while we found it 6.0 points higher. Similarly, 48 per cent. of their observations varied within  $\pm 2.5$  points of their average and 87 per cent. within  $\pm 7.5$  while 45 per cent. of our observations varied within  $\pm 2.0$  points of our average and 88 per cent. were within  $\pm 6$  points.

We also studied our cases to see whether those in whom the difference in the two methods was either much greater or much less than the average difference, were all of one sex or of one nutritional extreme. No such relationship was found.

We next determined the average difference between Harris-Benedict and Du Bois deviations in separate groups of patients. We divided the whole series into fourteen groups according to the deviations by the Du Bois method. Each group covered a range of ten points. We then determined the average (Du Bois)—(Harris-Benedict) difference for each group. The results are indicated by the interrupted diagonal line in Figure 1. While the average difference for the whole series, as has been said, was 6.0 points, it will be seen that at the lower end, that is to

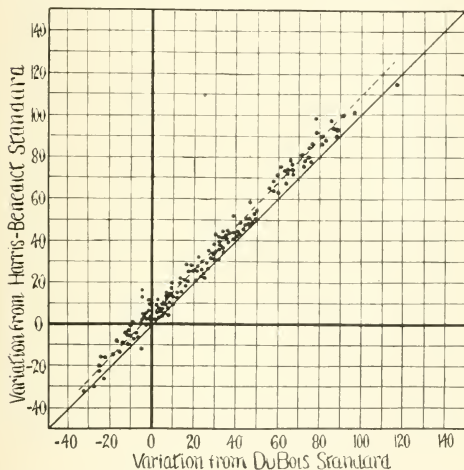


Fig. 1.—Basal metabolism deviations of 160 patients by the Harris-Benedict (ordinates) and Du Bois height-weight formula (abscissae). The per cent. deviation above or below the predicted metabolism is shown on the margin. The interrupted line represents the average of the individual points.

say in the neighborhood of a deviation of  $-20$  per cent. it is only 4 points, while at the upper end in the neighborhood of a deviation of  $+80$  per cent. it is 8 points. In this connection it will be remembered that in the Carpenter series of normal men the Harris-Benedict deviation averaged 2.15 points higher than the Du Bois (Table 1).

These relationships we believe are interesting, for they seem to show that there is no fundamental difference in principle between the

Du Bois and the Harris-Benedict methods. Indeed, as Boothby and Sandiford have properly pointed out, the two methods are constructed on identical factors, stature, weight, sex and age. The difference in the two methods is essentially merely a systematic difference in the selected standards. The Sage Institute standards throughout are a little higher than the Harris-Benedict. This, as Du Bois has suggested to us in a recent letter, may have been because most of the subjects used in making the Sage standards were observed in hourly periods in the calorimeter,

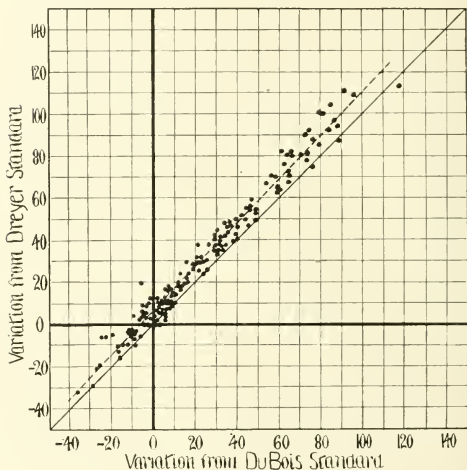


Fig. 2.—The same for the Dreyer and Du Bois formulas.

while a considerable number of Benedict's were observed in short periods with respiration apparatus. As Du Bois further suggests it is not improbable that the subjects were slightly quieter during the shorter periods.

As a matter of fact what all this boils down to is that if approximately 1.8 calories be subtracted from each of the Sage Institute standards, and if they then be employed as before, the results obtained in this series of patients will be essentially like those obtained by the Harris-Benedict method, that is to say, the (Harris-Benedict)—(Du

Bois) difference will be within  $\pm 2$  points in about 40 per cent. of the cases, and within  $\pm 6$  points in about 85 per cent. more. Furthermore, the difference will be just as likely to be positive as negative.

We next compared the deviation by the Du Bois and Dreyer methods. The results are shown in Figure 2. They are very similar to those of Figure 1. The Dreyer deviations averaged 7.3 points higher than the Du Bois. Thirty-eight per cent. of the Du Bois-Dreyer differ-

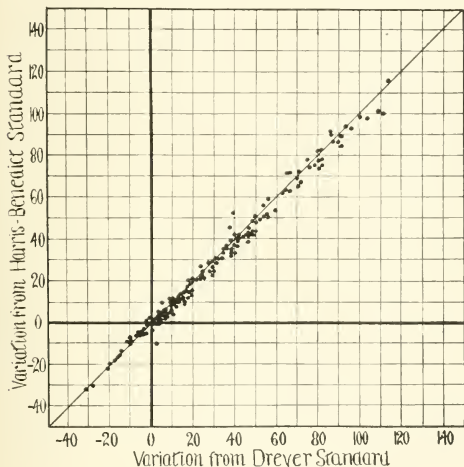


Fig. 3.—The same for the Harris-Benedict and Dreyer formulas.

ences varied within  $\pm 2$  points of the average difference and 75 per cent. within  $\pm 6$  points.

A comparison of Dreyer deviations with Harris-Benedict deviations is given in Figure 3. It shows a very striking parallelism between the two methods. The Dreyer averaged 1.3 points higher than the Harris-Benedict, and 66 per cent. of the differences were within  $\pm 2$  points of the average difference and 88 per cent. within  $\pm 4$  points.

#### DISCUSSION

We are now in a position to discuss the relative merits of the Du Bois, the Harris-Benedict, and the Dreyer methods, at least in so far



as they concern the clinician who wishes to get an accurate idea of the degree of abnormality of his patients' basal metabolism.

In predicting the metabolism of normal men it was found that the three methods gave about equally good results, that in predicting that of obese subjects the Harris-Benedict method gave slightly better results than the other two. In the matter of deviations from normal in patients with myxedema, toxic goiter and the like, it was found that the information gained by the three methods was again strikingly similar.

The deviations by the Du Bois method are consistently somewhat less than those by the other two, but as has been pointed out this difference can be abolished by a slight change in the Sage Institute standards. These standards are probably too high by somewhere between 1.8 and 0.6 calories. It is only fair to call attention to the fact that Du Bois and his co-workers have said in print that the standards would have to be revised from time to time as more and more normal data accumulated.<sup>16</sup>

We have yet to answer the original question, which method should the clinical calorimetrist use. The answer is obviously that in one sense it is really of small consequence which he uses since the results obtained with the three are so similar. Uniformity, however, is always advantageous and it is best not to abandon an old method for a new one, unless the new presents some material advantage over the old. The Du Bois method is the one in common use today. Since neither the Harris-Benedict nor the Dreyer methods have made any material improvement on it we believe it wise to continue with it, and especially in view of the fact that the existence of calorimetry in the clinic of today is due in large measure to the work of Du Bois. He was the first to devise a satisfactory surface area formula, and also the first to provide standard figures for normal metabolism, both of which were necessary before calorimetry could be added to the diagnostic armamentarium of the clinic or to the list of tests of function.

#### SUMMARY AND CONCLUSIONS

1. The accuracy of prediction of the basal metabolism of normal men by the Du Bois height-weight surface area method, the Harris-Benedict multiple prediction tables and by the Dreyer body weight formula, have been compared. It was concluded that the average deviation was essentially the same by each, though the Du Bois deviations tended to run about two points or more lower than either of the others.

2. The same study was made in a series of six obese subjects. It was found that with them the Harris-Benedict method gave a slightly

closer prediction than the other two. In general, however, the deviations by all three methods were within what may be considered a normal limit of variation in all of the six subjects. This furnishes confirmation of the conclusions drawn in earlier papers that there is no fundamental change in basal metabolism in simple obesity.

3. In abnormal subjects patients with hypothyroidism or hyperthyroidism, for example, it was found that the deviations by the three methods were essentially parallel, though on an average the Harris-Benedict deviation tended to be about 6 per cent. higher and the Dreyer about 7 per cent. higher than the Du Bois. It was pointed out that these differences could be practically abolished by a slight reduction in the Sage standards.

4. It is suggested, that although the deviation by the three methods are very similar, nevertheless, it is desirable to have uniformity, and that, therefore, the Du Bois method be continued, since it already is in common use and since the others appear to possess no material advantage over it.

## THE BLOOD UREA NITROGEN IN ACUTE INTESTINAL OBSTRUCTION

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The subject of acute intestinal obstruction has attracted interest for a considerable time both from a clinical and experimental standpoint. Ever since it was found that acute intestinal obstruction was amenable to operative therapeutics, surgeons have urged the early diagnosis of this condition, because they had learned that the success of their operative procedures was largely dependent on relieving the obstruction before the toxemia, which so conspicuously accompanies this condition, overwhelms the patient. The early recognition of acute intestinal obstruction, however, not infrequently presents difficulties even to skilled and experienced observers, chiefly due to the absence of the classical symptoms of the disease which often do not make their appearance until the intoxication has advanced to an alarming degree. In recent years the development of blood chemistry methods and their application, first, in clinical cases, and, later, in experimental cases of intestinal obstruction, have shown a striking elevation in the blood urea nitrogen and noncoagulable nitrogen, and have suggested the possible value of these determinations in diagnosis. The purpose of this communication is to describe a brief series of cases of acute intestinal obstruction and to report the observations which were made on the blood urea nitrogen.

In 1914, Tileston and Comfort,<sup>1</sup> in the course of a study of the blood chemistry in a large series of miscellaneous cases in human beings, found that in three cases of acute intestinal obstruction there was a surprisingly high elevation of the blood urea nitrogen and noncoagulable nitrogen. In these cases the blood urea nitrogen varied from 59 to 77 per cent. of the total noncoagulable nitrogen. Their highest blood urea nitrogen in a case of obstruction terminating in recovery was 92 mg. per 100 c.c. and their lowest reading was 45.5 mg. In a case of acute obstruction due to an intestinal band which terminated fatally in spite of operation, the blood urea nitrogen rose from 72.8 mg. at the time of operation to 114 mg. immediately prior to death. The phenol-sulphonephthalein excretion was determined in two cases. In the first case it varied from 25 to 43 per cent., whereas in the second case it was 70 per cent. in 2 hours and 10 minutes.

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1. Tileston, W., and Comfort, C. W.: Arch. Int. Med. **14**:620 (Nov.) 1914.

The study of the blood chemistry in acute intestinal obstruction was then taken up by Cooke, Rodenpaugh and Whipple,<sup>2</sup> who investigated the subject from an experimental basis. They produced acute intestinal obstruction and closed intestinal loops in dogs, and found that in the vast majority of cases there was a definite increase in the noncoagulable nitrogen which was apt to be more striking and constant in the cases associated with symptoms of acute intoxication. They were of the opinion that the determination of the noncoagulable nitrogen was of more value than the blood urea nitrogen, as the former was more uniformly elevated in cases of acute intestinal obstruction, whereas the latter in their series of cases varied from 30 to 60 per cent. of the total noncoagulable nitrogen. They believed that the determination of the noncoagulable nitrogen might be of value in the diagnosis and prognosis of human cases.

Whipple and his co-workers, in addition to many contributions on the nature of the substance responsible for the toxemia which is such an impressive feature of the clinical picture of acute intestinal obstruction, have studied the renal function in cases of experimental obstruction and proteose intoxication. McQuarrie and Whipple<sup>3</sup> found that associated with the intoxication of acute intestinal obstruction there exists a definite impairment of the excretory function of the kidney, as shown by a decrease in the ratio of urea and sodium chlorid excretion and a decrease in the percentage output of phenolsulphonephthalein. It is interesting to note that the alteration in the urea and sodium chlorid excretion is far more pronounced than the decrease in the excretion of phenolsulphonephthalein, and that a marked decrease in the output of the dyestuff occurred mainly immediately before death.

McQuarrie and Whipple<sup>4</sup> then studied the renal function as influenced by proteose intoxication, and found that when toxic proteose material obtained from a closed intestinal loop was injected intravenously, there followed a definite lowering of the excretory function of the kidney similar to that observed in experimental intestinal obstruction. Injection of other proteose substances obtained from various sources did not have this effect on renal function. This work of McQuarrie and Whipple is of particular interest in connection with studies by Longcope and Rackemann<sup>5</sup> of renal function in cases of hypersensitive individuals. They found that in three of six cases of urticaria, four of which were hypersensitive to one or more foreign

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2. Cooke, J. V.; Rodenpaugh, F. H., and Whipple, G. H.: *J. Exper. M.* **23**:717, 1916.

3. McQuarrie, I., and Whipple, G. H.: *J. Exper. M.* **29**:397, 1919.

4. McQuarrie, I., and Whipple, G. H.: *J. Exper. M.* **29**:421, 1919.

5. Longcope, W. T., and Rackemann, F. H.: *J. Urol.* **1**:351, 1917.

proteins, there was a definite disturbance in the functional activity of the kidney. One of the cases reported by Longcope and Rackemann was admitted to the hospital with the diagnosis of uremia and the finding of a blood urea nitrogen of 150 mg. per 100 c.c. at first seemed to confirm this diagnosis. The subsequent clinical course, however, showed that the case was one of sensitization to foreign protein and that the urea retention was probably due to proteose intoxication and its effect upon protein catabolism and renal function.

The group of cases which are herewith reported are seven in number and with two exceptions are cases of acute intestinal obstruction occurring after operation for some surgical disease of the abdomen. The first of the ante-operative cases was a woman aged 56 years who was ill for seven days with vomiting and marked abdominal distention and in whom operation revealed an annular carcinoma of the sigmoid. The second of the ante-operative cases was a woman 57 years old who was being treated in the hospital for a severe form of diabetes. While under observation, she developed marked obstipation and abdominal distention, and operation showed marked distention of small intestine with fecal impaction in the colon. All of the postoperative cases of intestinal obstruction, with one exception, terminated fatally, and post-mortem examination was obtained in all but one of the fatal cases. In the case in which necropsy was not permitted, the patient succumbed three weeks later to the continuous loss of fluid and presumably nutriment through the enterostomy wound. The blood chemistry determination which was done in all cases was the blood urea nitrogen by Van Slyke and Cullen's modification of Marshall's method. The non-coagulable nitrogen was not done. In one case the phenolsulphone-phthalein excretion was studied.

#### REPORT OF CASES

CASE 1.—E. B., female, aged 32 years, was admitted to the Presbyterian Hospital March 22, 1919, with the complaint of severe pain in the epigastrium, radiating around the right costal margin into the back. Pain was of two days' duration and was accompanied by repeated vomiting. The stools were light colored, and the urine was dark amber. She had had several similar attacks during the past ten years.

Physical examination showed jaundiced sclerae and tenderness in the right upper quadrant.

Patient was operated on March 24, 1919, and a chronically inflamed and contracted gallbladder, bound down by adhesions to the liver and pylorus, was found. There were several gallstones in the gallbladder, one in the common duct and three at the papilla of Vater. The common duct was opened, the stones were removed and the duct closed. The gallbladder was removed in the usual fashion and a rubber drain placed in Morrison's pouch.

March 24. Patient has made a fairly good immediate recovery from operation. She has vomited small amounts of bile tinged fluid but is otherwise comfortable.

March 25. Patient does not look well. Pulse is 110 and easily compressible. There is a moderate degree of distention. She looks toxic.

March 26. Patient is very much worse. Her eyes are sunken, facies is drawn, and she looks profoundly toxic. Abdomen is not markedly distended and is only slightly tender. She has vomited about 30 c.c. of dark-brown fluid, but passage of stomach tube returned a large amount of almost black fluid with odor of upper intestinal material. Pulse is 140 and is very soft in quality. Colon irrigation returns clear with slight flatus.

March 30. Patient is irrational, and pulse is small and rapid. She is vomiting repeatedly. Abdominal distention and tenderness are very slight. She has no pain in her abdomen.

April 3. Blood urea nitrogen, 147 mg. per 100 c.c.; hemoglobin, 80 per cent.; red blood cells, 5,200,000; white blood cells, 30,000; polymorphonuclears, 87 per cent.; lymphocytes, 13 per cent.

April 4: The patient was seen in consultation by the medical service who found no evidence of chronic renal trouble or chronic disease as a basis for the patient's condition. It was felt that the high blood urea nitrogen was due to acute renal insufficiency which was thought to be due to some underlying disturbance of undetermined nature.

April 5. Condition of patient is distinctly improved. Color is better and eyes are brighter. Blood urea nitrogen, 132 mg. per 100 c.c.

April 7. Patient feels a great deal better but complains of intense itching from hives. Examination shows a marked generalized eruption of urticarial character.

April 8. Blood urea nitrogen, 50 mg. per 100 c.c.

April 10. Eruption has disappeared entirely. Patient is well on the road to recovery, and is eating with considerable appetite.

April 23. Patient was discharged feeling fine.

April 22, 1920. Patient was seen in the follow-up clinic and found to be in excellent health.

The clinical picture which this patient presented was very confusing, and, except for the frequent vomiting, was not typical of intestinal obstruction. The blood urea nitrogen was, therefore, of great interest as pointing to this condition as the cause of the patient's toxemia, and although the exact nature of the obstruction was not determined, there is little conjecture as to its existence. An unusual feature of the case was the appearance of an urticarial eruption during the convalescence of the patient. In the light of Whipple's work on the nature of the substance responsible for the toxemia of intestinal obstruction and the well recognized rôle of foreign proteins in the production of cutaneous lesions, it seems fair to assume that the urticarial eruption was simply a manifestation of proteose intoxication subsequent to the intestinal obstruction.

CASE 2.—H. P., male, aged 21 years, was admitted to the Presbyterian Hospital, Jan. 17, 1920, with the complaint of pain in the abdomen of thirty-six hours duration. The pain was first situated in the epigastrium where it was dull in character, but two hours later it localized in the right lower quadrant where it became sharp and cramplike. He vomited several times after the onset of the pain.

Physical examination showed definite right rectus rigidity with a marked degree of localized tenderness over McBurney's point. White blood cells, 17,500; polymorphonuclears, 90 per cent.; lymphocytes, 10 per cent. Urine: amber, clear, acid, specific gravity, 1.024; albumin, 0; glucose, 0; microscopic, negative. Operation Jan. 17, 1920, showed an acutely inflamed appendix with a perforation in its middle third and considerable free fluid in the pelvis. Appendix was removed in the usual fashion and rubber-tube drains inserted into the pelvis.

January 18. Patient has made a good recovery from operation without nausea or vomiting. There is no distention.

January 19. There is no distention and patient is very comfortable.

January 21. Patient has been considerably distended for the past thirty-six hours and is complaining of severe cramplike abdominal pain. There has been no relief from rectal treatments. Pulse has increased from 100 to 120 and the patient looks badly. He has vomited large amounts of brownish material several times.

January 22. All of the patient's symptoms have increased in severity. Blood urea nitrogen, 54 mg. per 100 c.c.

January 23. Patient was operated on and the small intestine was found to be greatly distended and congested, whereas the large intestine was completely collapsed. No acute change from distended to collapsed intestine was found, there being a gradual transition from nondistended ileum at the ileocolic junction to a point about 3 feet proximal to the cecum where the ileum was distended to twice its normal diameter. It was felt that in separating the coils of intestine from the drainage tubes, a mechanical obstruction had been relieved before its exact nature could be studied. Enterostomy tube was inserted into the ileum about 2 feet above the ileocecal junction.

The patient had a very stormy postoperative course which finally terminated fatally twenty days after his second operation. He developed a severe pneumonitis from which he recovered only to lapse into a stage of marked inanition due to continuous loss of fluid and nutriment through his enterostomy wound. All attempts to divert the stream of intestinal contents into the distal loop of enterostomy were futile.

This case presented a straightforward picture of acute intestinal obstruction with all the cardinal symptoms. The finding of a blood urea nitrogen of 54 mg. in the absence of any signs of pre-existing renal disease confirmed the clinical diagnosis.

CASE 3.—W. H., male, aged 49 years, was admitted to the Presbyterian Hospital, Feb. 10, 1920, with the complaint of pain in the lower abdomen of twenty-four hours' duration. One week previously he had been ill for three days with a streptococcus sore throat from which he had apparently recovered. He became nauseated and vomited several times shortly after the onset of the pain.

Physical examination showed moderate degree of abdominal distention with tenderness in both lower quadrants. White blood cells, 14,400; polymorphonuclears, 89 per cent.; lymphocytes, 11 per cent. Urine: amber, clear, acid; specific gravity, 1.034; albumin, 0; glucose, 0; microscopic, negative.

Operation Feb. 10, 1920, showed an acutely inflamed appendix extending across the abdomen to the left wall of the pelvis, where it was adherent, binding down and obstructing the sigmoid. Small intestine and large intestine above the level of the obstruction were greatly distended. The appendix was removed in the usual fashion and rubber tube drains inserted in the pelvis.

February 11. The patient made a fairly good recovery from operation but is still distended. Colon irrigations returned a moderate amount of gas and fecal matter.

February 16. Distention is very marked, in spite of all treatment. Patient has grown weaker, and pulse has grown more rapid and is of poorer quality. A secondary operation was performed this morning, and an enterostomy tube inserted into the presenting loop of dilated small intestine. On account of patient's condition, exploration was not performed, but small intestine appeared greatly distended.

February 18. Enterostomy tube is draining freely, but patient's condition has grown worse. He is apathetic, weak and has occasional twitching of the arms. Blood pressure: systolic, 92; diastolic, 68. Urinary output for the past twenty-four hours has been only 50 c.c. in spite of an intake of 2,500 c.c. of fluid given intravenously and by hypodermoclysis. Blood urea nitrogen, 106 mg. per 100 c.c.

February 19. Patient is comatose. Breathing is stertorous. Pulse is slow and quite full. There has been complete anuria for the past twenty-four hours. Blood urea nitrogen, 170 mg. per 100 c.c. Patient died that afternoon.

Necropsy showed marked distention of the stomach and jejunum above the level of the jejunostomy. Below this the intestine was collapsed. No definite organic obstruction was demonstrated. The kidneys together weighed 270 gm. They were normal in size and slightly softer than usual. The capsule was glistening and stripped easily. External surface of kidneys showed evidence of lobulation and was irregularly congested. On cut section the striations were easily made out, but between the striations there seemed to be swelling of cortical tissue. Glomeruli were easily visible as shiny points. Medulla and pyramids were normal. Microscopic examination showed a few areas where the glomeruli were fibrosed with collapse of adjacent tubules. Throughout the remainder of the sections the glomeruli were congested and completely filled their capsules, but there were no adhesions between glomerulus and capsule. The convoluted tubules were slightly swollen so that their lumens were small, but cell outlines and nuclei were well preserved.

This case, although undoubtedly one of acute intestinal obstruction, is puzzling in so far as the cause of the obstruction was not determined. It was at first believed that it was one of paralytic ileus, and the absence of cramps and visible peristalsis supported this belief. However, the fact that all colon irrigations returned without gas or fecal material pointed to the presence of a complete obstruction of organic nature, and this impression was confirmed by the postmortem findings of distention of the upper jejunum and collapse of the remainder of the intestine. A striking feature of the clinical picture was the marked decrease in the excretory function of the kidney, as shown by the almost complete anuria which lasted for a period of forty-eight hours prior to death. Associated with this renal insufficiency he developed involuntary twitchings of the arms not unlike those seen in uremic states, and later lapsed into a condition of coma. These symptoms were not the result of any inflammatory process in the kidney, as pathological examination failed to show any of the morphological changes which usually accompany nephritis, but were due to the lowering of renal function which follows intestinal obstruction and proteose intoxication.

CASE 4.—M. J., female, aged 60 years, entered the Presbyterian Hospital, March 6, 1920, with the complaint of passage of bright red blood from the rectum of three months' duration.



Physical examination was essentially negative, except for the presence of a hard mass situated on the anterior rectal wall, which pathologic examination showed to be a typical adenocarcinoma. March 11, 1920, the rectum and the lower portion of the sigmoid were removed by the combined abdominoperineal method. During the latter part of the operation, the patient went into a state of shock presumably on account of traction on the mesentery. She remained in this state for approximately thirty-six hours, and then gradually lapsed into an apathetic stage interrupted by occasional periods of restlessness. She refused food constantly and fluids were administered by infusion and hypodermoclysis. Feedings through stomach tube were futile, as they were vomited shortly afterward. Distention was moderate, but there were no cramps or visible peristalsis. Blood urea nitrogen, March 17, was 99 mg. per 100 c.c. Blood pressure: systolic, 115; diastolic, 70. Urine showed a faint trace of albumin but was otherwise negative. Specific gravity varied from 1.018 to 1.012. Patient grew steadily worse and died April 4, 1920.

Necropsy showed a loop of small intestine adherent to parietal peritoneum at upper part of operative incision. Above this level the small intestine was moderately distended with fluid and gas. Below the level of the obstruction the intestine was collapsed. The kidneys together weighed 300 gm. They were flabby and of equal size. Left kidney showed that the capsule stripped easily exposing a slightly rough, pale pink surface. About the middle of the organ there was a mottled reddish-yellow scar which on section appeared to be an old infarct. The cortex measured 4 mm. in width and was pale with inconspicuous glomeruli. The striations were indefinite but many straight congested vessels were seen in the cortex. Medulla was grossly normal. Pelvis was considerably dilated and congested in streaks. The right kidney presented the same appearance except for the absence of any infarct. Microscopic examination showed the glomeruli and tubules to be normal. There were no changes in the blood vessels. Section through the old infarct in the left kidney showed an area of coagulation necrosis extending from cortex into peripheral portion of medulla. Shadows of glomeruli and tubules were still present.

CASE 5.—A. R., female, aged 62 years, entered the Presbyterian Hospital, April 4, 1920, with the complaint of pain in the abdomen, cramps and vomiting of twenty-four hours' duration. For the past fourteen years she had had an umbilical hernia which had always been easily reducible until forty-eight hours ago when she found that she could not replace the mass within the abdomen.

Physical examination showed a profoundly toxic, elderly woman with a greatly distended abdomen. At the umbilicus there was a large, tender irreducible hernia.

Operation was performed April 4, 1920. The contents of the hernial sac was the entire transverse colon, which was so greatly distended with gas that it had to be punctured twice before it could be returned to the abdominal cavity. The patient made a good recovery from operation and was in excellent condition for three days. On the fourth day she began to look poorly, and the abdomen was considerably distended. She appeared to be listless and apathetic, and these symptoms grew steadily worse. April 10, 1920, blood urea nitrogen, 140 mg. per 100 c.c. April 12, 1920 the patient was given a hypodermoclysis of 1,000 c.c. of physiologic sodium chlorid solution and at the end of the treatment 6 mg. of phenolsulphonephthalein was given intramuscularly, after the patient had been previously catheterized. At the end of two hours and ten minutes, patient was again catheterized and 230 c.c. of urine obtained. Phthalein excretion was 58 per cent. Blood urea nitrogen on the same day was 130 mg. Blood pressure was not elevated. April 9, 1920: systolic, 135; diastolic, 70. April 11, 1920: systolic, 130; diastolic, 65. Urine examination was completely negative. There was no albumin and no casts. Specific gravity varied from 1.014 to 1.026. The patient's condition grew progressively worse and she died on April 14, 1920.

Necropsy showed the colon to be collapsed from the hepatic flexure to the rectum. At the hepatic flexure there were a few relatively firm adhesions, and this was found to be the site where the intestine had been punctured during operation. Above this point the colon and small intestine were tremendously distended. The kidneys together weighed 280 gm. They were of equal size and similar in appearance. The capsule stripped easily exposing a gray surface with distended stellate veins. On section, the cortex was normal in width with distinct striations. The glomeruli were normally prominent. In the lower pole of the right kidney there was a small, yellow rectangular infarct. Microscopic examination showed the tissue to be poorly preserved, probably through postmortem changes. The glomeruli were normal, except for occasional slight thickening of the capsule. The tubules presented no abnormality. There were no changes in blood vessels. Section through infarct showed an area of coagulation necrosis extensively infiltrated with red blood cells.

## ANALYSIS OF URINE AND BLOOD

Case	Name	Age	Date	Urine			Blood Urea N. Mg. per 100 C.c.	Blood Pressure	Remarks
				Specific Gravity	Albumin	Casts			
1	E. B.	32	4/ 3/19	1.030	+	0	147	.....	Acute ileus following cholecystectomy and common duct drainage; obstruction relieved spontaneously
			4/ 5/19	1.021	++	0	132		
			4/ 8/19	1.022	++	0	50		
2	H. P.	21	1/22/20	1.024	0	0	54	.. ..	Acute ileus following appendicectomy with drainage; obstruction in region of ileocecal junction
3	W. H.	49	2 18/20	1.034	0	0	106	92/68	Acute ileus following appendicectomy with drainage; obstruction in lower jejunum
			2 19/20	Q.N.S.	+	0	170	94 60	
4	M. J.	60	3/17/20	1.018	+	0	99	115/70	Acute ileus following resection of carcinoma of rectum; upper intestinal obstruction due to adhesions
5	A. R.	62	4/10/20	1.026	0	0	140	135 70	Acute ileus following repair of strangulated umbilical hernia; obstruction at hepatic flexure of colon
			4/12/20	1.014	0	0	130	130/65	
6	A. B.	56	4/21/20	1.018	+	+	74	98 75	Acute ileus due to a constricting annular carcinoma of sigmoid
7	A. M.	57	10/26/20	1.012	0	0	60	145 105	Acute ileus due to fecal impaction in colon

In this case the question arose as to whether or not the high blood urea nitrogen might be caused by a chronic nephritis. Against this diagnosis was the absence of high blood pressure, the negative urinary findings, with a variation in specific gravity from 1.014 to 1.026 and a phenolsulphonephthalein excretion of 58 per cent. It was felt that if the elevation of the blood urea nitrogen were due to a chronic nephritis, the phthalein excretion would be greatly lowered, whereas in acute intestinal obstruction as shown by McQuarrie and Whipple, the phthalein excretion is not greatly altered until shortly before death.

CASE 6.—A. B., female, aged 56 years, entered the Presbyterian Hospital with the complaint of distention of the abdomen of one week's duration.

Physical examination showed a profoundly ill, elderly woman with an enormously distended abdomen. There was no visible peristalsis. Blood pressure was 98 systolic and 75 diastolic. White blood cells, 11,600; polymorphonuclears, 77 per cent.; lymphocytes, 23 per cent. Urine showed a very faint trace of albumin with a rare finely granular cast. Blood urea nitrogen was 74 mg. per 100 c.c. Operation was performed April 21, 1920, and showed an annular

carcinoma of the sigmoid with tremendous distention of the intestine above this level. There was a small perforation in the transverse colon. This was closed and a large enterostomy tube inserted in the descending colon. Although the patient stood the operation well, she lapsed into a state of marked apathy and died six hours later. No necropsy was obtained, but it was felt that in the absence of any signs pointing to chronic nephritis, the high blood urea nitrogen was due to the toxemia of intestinal obstruction. This case, as did the preceding one, demonstrated that an elevation of the blood urea nitrogen can occur following a low obstruction as well as a high intestinal obstruction.

CASE 7.—A. M., female, aged 57 years, entered the Presbyterian Hospital, July 7, 1920, with the complaint of weakness, loss of weight, polydipsia and polyuria of five months' duration. Urine examination showed glucose 2.6 per cent. and the blood sugar was 0.43 per cent. She was fasted for several days and placed on a restricted diet under the influence of which she gradually became sugar free. Oct. 22, 1920, she complained of severe abdominal cramps and obstipation. She was given catharsis without effect and enemas were returned clear. After four days of marked abdominal distention, cramps and failure to pass either gas or feces, the patient was operated on, and the large intestine found filled with impacted fecal material while the small intestine was greatly distended with gas. Blood urea nitrogen taken the day before operation was 60 mg. per 100 c.c. The patient was in very poor shape at time of operation, and died shortly afterward. Blood urea nitrogen previous to onset of obstipation was not done, as the patient was apparently an uncomplicated diabetic, but it was felt, nevertheless, that the blood urea nitrogen of 60 mg. presented an abnormal elevation resulting from her ileus.

#### SUMMARY

Seven cases of acute intestinal obstruction are described, in all of which there was an increase in blood urea nitrogen. The lowest reading was 54 mg. per 100 c.c. The highest reading was 170 mg.

In one case in which the blood urea nitrogen was 130 mg. per 100 c.c., the phenolsulphonaphthalein excretion was studied and found to be 58 per cent. in two hours and ten minutes.

In one case a generalized urticarial eruption appeared while the patient was convalescing from an acute ileus. As the substance which causes the toxemia of acute intestinal obstruction is presumably of proteose nature, it was felt that this eruption was probably a cutaneous manifestation of proteose intoxication.

All cases were free from any evidence of chronic renal disease, and it is, therefore, fair to assume that the elevation in the blood urea nitrogen was the result of the acute intestinal obstruction.<sup>6</sup>

I wish to express my indebtedness to Dr. A. V. S. Lambert, Director of the Surgical Service, for the privilege of reporting these cases, to Dr. W. T. Longcope, Director of the Medical Service, for many helpful suggestions and to Dr. J. W. Jobling, Director of the Pathological Service for the use of the pathological material.

6. After this communication was in proof, an article by I. M. Rabinowitch was published in the Canadian Medical Association Journal for March, 1921, in which an increase in the blood urea nitrogen was reported in a series of cases of intestinal obstruction, acute general peritonitis and acute pancreatitis.

## BOOK REVIEWS

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LAENNEC APRES 1806; 1806-1826; D'APRES DES DOCUMENTS INEDITS. ALFRED ROUXEAU (Professeur à l'Ecole de médecine de Nantes). 80, Paris, 1920. J. B. Baillière et Fils, 19 Rue Hautefeuille, Fr. 35.

The publication in 1912 of the first volume of Professor Rouxeau's life of Laennec (Laennec avant 1806, etc. 80 Paris, 1912, J. B. Baillière et fils) was a happy event for those who cherish the memory of one of the great figures in the history of medicine. And now, after more than eight years, comes the conclusion. Filled with a just admiration of the man and his work, together with the pride of a compatriot in the accomplishments and contributions of a fellow Breton, generously aided by the living members of the Laennec family, Professor Rouxeau has gathered a remarkably full material bearing on the life and career of the discoverer of auscultation.

From a minute and judicial study of this material, and from a personal familiarity with the scenes which surrounded Laennec's boyhood, the author has constructed faithfully, lovingly, sympathetically, the narrative of his career. One follows step by step from boyhood onward the development of a great character. The wealth of quotation from personal letters gives one a rare insight into the spirit of the man, and lends a peculiar personal charm to the picture.

To Professor Rouxeau we owe a debt of sincere gratitude for weaving together so skilfully the threads of a story which should be familiar to every physician who loves the history of his art.

W. S. T.

WIENER ARCHIV FUER INNERE MEDIZIN. Herausgegeben von Priv.-Doz. DR. RICHARD BAUER, PROF. DR. RUDOLF JAKSCH, etc. GELEITET VON W. FALTA UND K. F. WENCKEBACH, Urban und Schwarzenberg, Berlin und Wien.

When the history of the work of physicians and biologists during the world war comes to be written, it will probably appear that one of the finest figures will be that of the modest, well trained and unselfish K. F. Wenckebach, who, called to the University of Vienna when it was an honor to be there, chose to remain when the sword of Brennus had made life almost impossible. What he and others have done to keep up the courage of the rest of the population we can dimly surmise. This new Archiv is a promising example of the spirit of the medical Viennese. The old format is retained, the old standpoint, clinical and experimental, if the experiment bears on a clinical problem. Fascicles of from ten to fifteen quires are expected at irregular periods, forming volumes of from thirty to forty quires. No price is given. How can it be in a country where paper money is of less value than beer bottle labels? No longer the good paper of old. Yet the type and presswork are good, the proofreading better than much of ours. The illustrations are few and only black and white.

The table of contents of Volume 2, Part 1, shows interesting material. Egmont Muenzer of Prague returns to the study of vascular sclerosis, in which he contrasts sclerosis of the larger and smaller (precapillary) arteries, and as a cause of arteriolo-capillary sclerosis he suggests acute infectious disease and gout.

Edmund Maliwa and Miss Eckert of Innsbruck have an article concerning chlorin metabolism in histogene edemas, with a criticism of Ambard's law on the relation between chlorid concentration in serum and excretion in urine. They think the law is not valid in edemas, but applies after their removal.

Arnold Kirch of Vienna writes on concretion and accretio cordis. He takes a case wrongly diagnosed by Baemler to show how easy it is to make a mistake, so that concretion may be diagnosed and the necropsy show no signs; on the other hand, the necropsy gives the first intimation. He speaks of the signs advanced by various authorities, such as absence of systolic apex beat, rebound of the thorax, diastolic filling of cervical veins, Broadbent's sign, immobility of apex beat and dulness on change of position, paradox pulse, metallic heart sounds, constant doubling of the second sound at the apex and the work of Wenckebach with relation to the movement of the thorax. The author advances a new pulse sign—a small pulse easily compressed by the finger, and with low pressure and low pulse pressure (from 10 to 15 mm.). He thinks the condition is usually the sequel of a polyserositis, especially tuberculosis.

Alfred Decastello writes on bacteriemia in typhoid and its treatment by vaccines. He asserts that under vaccine treatment the bacilli disappear from the circulation before the fever, and that at the same time rapid removal of typhoid bacilli takes place from the internal organs. In some cases no such results occur. Success depends on the antibacterial effect, the factors for which cannot yet be stated.

F. Hoegler reports from Falta's clinic a case of chronic polyneuromyositis with severe contractures, giving the differential diagnosis from trichinosis, polymyositis, polynuritis and muscular atrophy.

Oskar Wellmann in Chvostek's clinic describes the iodine binding power of urine and thinks it gives a useful measure for the analysis of kidney function equal in value to specific gravity. The same author writes on the pathology of edema disease, showing that the pancreas serves as a point of predilection for alimentary poisons.

S. Bondy and R. Strisower, working under Pal, speak of the effect of hypertonic salt solution on hemoglobinuria from cold.

Egon Weiser contributes an article from the German medical clinic of Prague, showing that political frontiers cannot prevent cultural associations, on insufficient expansibility of the heart as a cause of severe circulatory disturbance, with an interesting study of the probable mechanism.

Needless to say, the *Wiener Archiv* must be included among current journals in all medical libraries and its contents examined regardless of the fates of archdukes and kaisers or the rise and fall of kronen.

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#### CORRECTION

In the paper by C. M. Richter, published in the March issue of the ARCHIVES OF INTERNAL MEDICINE, the legend for Figure 3 was omitted. It reads: Continuous line represents air pressure figures taken at 8 a. m. (Washington, D. C., time) every day, reduced to sea level and standard gravity. Weekly lines give number of deaths from influenza and pneumonia.

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## THE INCIDENCE AND HISTOPATHOLOGY OF TUBERCULOSIS OF THE TONSILS

BASED ON EIGHT THOUSAND SIX HUNDRED TONSILLECTOMIES.\*

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An unusual opportunity to study the less common pathologic changes in the tonsil has been afforded in the department of pathology of the University of Michigan through the practice of making routine histologic examinations of all tonsils received from the University Hospitals. This material now represents approximately 9,000 cases. This is a far larger series than has been reported from the standpoint of a microscopic study hitherto, and lends itself to quantitative analysis with the prospect of yielding much more accurate results, within the limitations of the data considered, than the smaller numbers forming the basis of previous studies.

While tuberculosis occurs in but a small percentage of the tonsils examined, as compared to the various chronic inflammatory manifestations, hyperplasias and metaplasias, which are present in varying degrees in all tonsils, regardless of the clinical history, its occurrence is of sufficient frequency to constitute one of the chief reasons for continuing the labor involved in the routine histological examination of all tonsils received. It greatly outranks the other chronic infective granulomas; recognizable syphilitic lesions being next in order, but by no means as frequent, while actinomycosis of the tonsil ranks third in this group, although met with only very rarely.

This paper deals with two aspects of tonsil tuberculosis. First, (a) the total incidence will be considered, with the effect on the incidence of the character of the population from which the cases are drawn; (b) the incidence in various age groups, and (c) the incidence as to sex. In the second part of the paper, the histopathology of tuberculosis of the tonsil will be discussed and the cases separated into a limited number of groups showing lesions of quite different character in each group and having an entirely different clinical significance in each instance.

### LITERATURE

A complete survey of the literature is unnecessary at the present time, but reference will be made to all important articles in their proper connection and a rather extensive bibliography is appended.

\*From the Department of Pathology University of Michigan.

The literature of tuberculosis of the tonsils is of comparatively recent date. This is due, in part, to Virchow's (1864) statement, quoted in most of the older textbooks, to the effect that tuberculosis of the tonsil had not yet been observed. Much more important in this connection, however, is the fact that, in its most common forms, tuberculosis of the tonsil cannot be diagnosed macroscopically, and, therefore, becomes the subject of report only as histologic examinations are more frequently made. The earliest observations seem to be those of Cornil<sup>1</sup> (1875), (Quoted by Friedmann<sup>2</sup>) who found an ulcerating lesion of the pharynx and tonsil in an otherwise healthy appearing individual; of Deplous<sup>3</sup> (1878), who found a tuberculous ulceration of the tonsil as well as of the adjacent parts in a child dying of pulmonary tuberculosis, and of Orth<sup>4</sup> who produced tonsil tuberculosis experimentally in dogs in the course of a series of feeding experiments with tuberculous tissues, apparently a primary focus.

Numerous articles have dealt with the occurrence of tonsil tuberculosis in necropsy material derived from patients dying with obvious tuberculosis lesions elsewhere in the body. Some of the more important of these are the papers of Strassmann,<sup>5</sup> Dmochowski,<sup>6</sup> Schlenker,<sup>7</sup> Krückmann,<sup>8</sup> Walsham,<sup>9</sup> Labbé and Lévi-Sirugue<sup>10</sup> and Friedmann. The frequency of secondary tonsil involvement in cases of advanced pulmonary tuberculosis was thus early established. The earliest reference to well authenticated cases of primary tuberculosis of the tonsil is that of Orth<sup>11</sup> who found characteristic microscopic lesions in the tonsils of children dying from diphtheria without evidence of tuberculosis elsewhere in the body.

1. Cornil: Quoted by Friedmann.<sup>2</sup>

2. Friedmann, F. F.: Ueber die Bedeutung der Gaumentonsillen von jungen Kindern als Eingangspforte für die tuberkulöse Infection, Beitr. z. path. Anat. **28**:66, 1900.

3. Quoted by Friedmann.<sup>2</sup>

4. Orth, J.: Experimentelle Untersuchungen über Fütterungstuberculose. Arch. f. path. Anat. u. Physiol. **76**:216, 1879.

5. Strassmann, F.: Ueber Tuberculose der Tonsillen, Arch. f. path. Anat. u. Physiol. **96**:319, 1884.

6. Dmochowski: Ueber secundäre Erkrankungen der Mandeln und der Balgdrüsen an der Zungenwurzel bei Schwindsüchtigen, Beitr. z. path. Anat. **10**:481, 1891.

7. Schlenker, E.: Beiträge zur Lehre von der menschlichen Tuberculose, Arch. f. path. Anat. u. Physiol. **134**:161, 1893.

8. Krückmann, E.: Ueber die Beziehungen der Tuberculose der Halslymphdrüsen zu der Tonsillen, Arch. f. path. Anat. **138**:534, 1894.

9. Walsham: Latent Tuberculosis of the Tonsil, Tr. Path. Soc. Lond. **49**:67, 1898.

10. Labbé and Lévi-Sirugue: Etude sur les lésions de l'amygdale dans quelques cas de tuberculose, Bull. Soc. Anat. de Par., 6 Serie **1**:919, 1899.

11. Orth: Lehrbuch der speciellen pathologischen Anatomie, 1887, p. 663.

The work of Lermoyez<sup>12</sup> drew attention to tuberculosis of the pharyngeal tonsils, and the papers of Pluder and Fischer,<sup>13</sup> McBride and Turner,<sup>14</sup> Brieger,<sup>15</sup> Piffel,<sup>16</sup> Rethi<sup>17</sup> and Hynitzsche,<sup>18</sup> among others, resulted. The occurrence of tonsil tuberculosis during childhood has been investigated especially by Latham,<sup>19</sup> Friedmann,<sup>2</sup> Ito,<sup>20</sup> Kingsford<sup>21</sup> and Mitchell.<sup>22</sup>

Of the important contributions dealing in a general way with the subject of tonsil tuberculosis, or with special phases of it, such as the tonsil as a point of entrance of infection; the nature of the infecting organism, whether bovine or human; relationship to lymphoid hyperplasia and relationship to cervical gland and pulmonary tuberculosis, the papers of Gottstein,<sup>23</sup> Grober,<sup>24</sup> Bandelier,<sup>25</sup> Carmichael,<sup>26</sup> Sewall,<sup>27</sup> Mitchell,<sup>28</sup> and of Crowe, Watkins and Rothholz<sup>29</sup> are especially worthy of mention.

12. Lermoyez, M.: Les végétations adénoïdes tuberculeuses, Presse méd. **3**:413, 1895.

13. Pluder and Fischer: Ueber primäre latente Tuberculose der Rachenmandelhyperplasie, Arch. f. Laryngol. u. Rhinol. **4**:372, 1896.

14. McBride and Turner: Nasopharyngeal Adenoids, Edinburgh M. J. **43**:355, 471, 598, 1897.

15. Brieger: Ueber die Beziehungen der Rachenmandelhyperplasie zur Tuberculose, Ztschr. f. Ohrenheilk. **33**:191, 1898.

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22. Mitchell, A. P.: Primary Tuberculosis of the Faucial Tonsils in Children, J. Pathol. & Bacteriol. **21**:248, 1917. Also J. Laryngol., Rhinol. & Otol. **33**:8, 40, 1918.

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## MATERIAL

The material used in this analysis consists of the faucial and pharyngeal tonsils from 8,697 consecutive cases, operated on in the University Hospitals and submitted to the pathologic laboratory of the University of Michigan for routine histologic examination. The period of time represented covers the years from 1906 to 1919, inclusive, but by far the greater part of the material has been received during the past five years. It may be stated roughly that the 8,697 cases indicate the examination of 8,697 pairs of faucial tonsils and of about one-fourth as many pharyngeal tonsils. While this is not strictly true, the instances in which only one faucial tonsil was removed or the pharyngeal tonsil alone was submitted for examination are so few that it makes no appreciable difference in the statistical analyses presented here, whether they are included or not.

The patients from whom these tonsils were removed were selected cases only to the extent that they all exhibited one or more of the conditions which have been accepted by many otolaryngologists during the past few years as indicating need for tonsillectomy. As a group, they are much more nearly representative of the total population of the region from which they came than is usually the case in similar studies. This is due to the peculiar character of the University Hospital which is in no sense a local clinic but draws its patients from the entire state and neighboring states as well. All ages, from one year to 78 years, are represented, the rural as well as the urban fraction of the population, and the extremes of social standing. Two groups of patients, however, have been sufficiently numerous to influence the curve of incidence of tuberculosis to an extent which will require further consideration in its proper place. These are the inmates of the state institutions for dependent and defective children, who at one time were brought almost en masse to the University Hospitals to have their tonsils removed; and university students, many of whom submit to tonsillectomy while resident in Ann Arbor. It may be noted here that this second group, coming for the greater part from comfortable middle class homes, has enjoyed living conditions free from those institutional risks to which the first has been subjected. Attention must also be called to the fact that in the last few years an increasing number of middle-aged patients have been referred to the otolaryngologist for tonsillectomy from other clinical departments. This, also, has had its influence upon the incidence of tonsillar tuberculosis.

## METHOD

Immediately on removal, the tonsils were placed in a 10 per cent solution of liquor formaldehydi and, after adequate fixation, portions were selected for microscopic examination. As a rule, all of the frag-

ments of the pharyngeal tonsil were embedded. The faucial tonsils were bisected in a vertical plane at right angles to the mucous surface, and from the cut face of one of the halves thus obtained the sections for microscopic examination were made. The other half was marked by attaching a numbered tag by means of a drop of thick gum acacia solution and dropped into a jar of alcohol for preservation in case it should be necessary to refer to it again. Usual methods of paraffin infiltration and embedding, and hematoxylin and eosin staining, were routinely employed, with the additional use of various special stains when indicated.

As a rule, only one or two sections were examined from each block, but care was taken to cover each section systematically in order that every field might be scrutinized. The blocks of adenoid tissue were sliced away until the largest possible sections could be obtained, and the half tonsils were embedded to cut from the entire flat surface, again giving the largest possible sections as well as those which would intersect the ramifications of the greatest number of crypts. A few sections, thus carefully oriented and systematically searched, will yield a higher percentage of positive results than serial sections of limited portions of the tonsil, for although tonsil tuberculosis is very often a local process involving only a small fraction of the entire organ, it is also very frequently a crypt infection, as will be pointed out later, hence it is important to examine some portion of each crypt as far as possible. We believe that our method accomplishes these purposes as satisfactorily as is possible with a limited number of sections.

The results, however, as expressed by the curve of incidence, represent minimal figures, for there can be no doubt that if it were possible to examine each tonsil throughout in serial sections taken at an interval of 0.1 mm. or less, the total number of cases would be increased by the addition of those in which single tubercles or small groups of tubercles would be found in the anterior and posterior peripheral portions of the tonsil. Sewall<sup>27</sup> and his associates attempted to estimate the percentage of error thus introduced by making serial sections of tonsils previously diagnosed as nontuberculous after the examination of a few sections. They found one case positive in the first series of twenty pairs examined and none in another series of twenty-three pairs, or 2.3 per cent. altogether. The percentage in 772 pairs examined by the original method was 3.9, which would seem to indicate that about 38 per cent. of the cases had been missed at first through incomplete examination. It is exceedingly dangerous, however, to assume from so occasional an occurrence as once in forty-three cases that the same ratio would hold throughout. Moreover, the original examination was made by a few frozen sections and there are no tissues in which diagnosis from frozen sections is more difficult than those of the lymph-adenoid group. It is

quite unlikely that the sections examined in the first instance would anywhere nearly approximate in size those obtained from the entire cut surface of a longitudinally bisected hyperplastic tonsil.

The method used here is the only one suitable for the routine examination of a large material, and there can be no doubt that the results are more accurate than those obtained from any other single method, except the examination of serial sections of the entire tonsil. The staining of direct smears from the cut surface yields of necessity but a very occasional positive result. It may, however, give false positives because of the occasional presence of tubercle bacilli in the tonsillar crypts without invasion of the tonsil itself. The examination of sections stained for tubercle bacilli is exceedingly laborious, requiring, oftentimes, the prolonged search of many sections, even when the tissue lesions are abundant. This method is of considerable value in confirming the histologic diagnosis in doubtful cases, but the results afforded by it can be accepted only when positive. Its limitations have been explained as due to the small number, or rapid disintegration, of the bacilli. It must also be borne in mind that after certain routine fixations, as, for instance, formol, staining of tubercle bacilli in sections is rendered either very difficult or impossible. The cultivation of the bacilli is a difficult procedure because of the prevalence of contaminating organisms and as a rule only a small portion of each tonsil can be employed in this method. Von Scheibner's<sup>30</sup> earlier results were all negative in a small series of twenty cases. Mitchell<sup>28</sup> seems to have attained a fair measure of success in his use of egg medium.

Animal inoculation has been much exploited as a method of investigation of tonsil tuberculosis since the report of Dieulafoy,<sup>31</sup> leading to his controversy with Cornil<sup>32</sup> as to the availability of this procedure. It is open to several serious objections; death of experimental animals from septic processes, false positives from surface organisms and those in the crypts, the small amount of tonsillar tissue which can be used, the failure to inoculate a sufficient number of organisms to overcome the resistance of the animal and the length of time necessary before the result can be ascertained. Special procedures have been devised to overcome some of these objections. Mitchell<sup>22</sup> employed a 2 per cent. aqueous solution of ericolin to effect a partial sterilization of the tonsil according to the method of Twort. Latham<sup>16</sup> used only the more central portions of the tonsil for inoculation. Von Scheibner<sup>30</sup> washed

30. Von Scheibner: Bilden die Tonsillen häufige Eingangspforten für die Tuberkelbacillen? Beitr. z. path. Anat. **26**:511, 1899. Also Deutsch. med. Wehnschr. **25**:343, 1899.

31. Dieulafoy: Tuberculose larvée des trois amygdales. Bull. de l'Acad. de méd., Par. **33**:437, 1895.

32. Cornil: Sur la tuberculose larvée de trois amygdales, La Semaine méd. **15**:223, 1895.

the tonsils in a dilute sublimate solution. The most elaborate method of all, that of Austin,<sup>33</sup> makes use of antiformin digestion and concentration of the minced and ground tonsil tissue, followed by injection into a traumatized inguinal lymph node of a guinea-pig. He found, however, but one positive in forty-five consecutive cases, contrasting with fifteen positive cases out of ninety-six as reported by Dieulafoy<sup>31</sup> in his use of this method without its later refinements. Even in the one case of Austin one might well question the results since the positive finding was obtained in only one guinea-pig which might have been previously infected with tuberculosis.

Against the purely histopathologic method of diagnosis of tonsil tuberculosis, the chief objection has been the supposed possibility of mistaking for tubercles the pseudotubercles resulting from the presence of mechanical foreign bodies or from organisms other than the bacillus tuberculosis. But as Sewall<sup>27</sup> points out, there is no more reason for questioning the etiology of a histological tubercle in the tonsil than in the lung, liver or spleen, in which situations diagnoses made from sections alone are constantly being accepted. We cannot, however, agree with him as to the relative infrequency of the foreign body pseudotubercle in the tonsil as indicated by his statement that in 1,544 tonsils examined not one "foreign body giant cell" was found. On the contrary, such giant cells occur with surprising frequency, but in them the provocative foreign body is usually to be found as a minute spicule, fiber or slender bristle, serving in itself to differentiate the cell as a true foreign body giant cell which, with whatever epithelioid or fibroblastic proliferation may accompany it, constitutes a foreign body pseudotubercle (Figs. 1 and 2). The difference in refraction and the lack of staining usually render such foreign bodies very easy of detection. The calcareous deposits rarely occurring in the giant cells of true tubercles must be borne in mind in this connection lest one fall into the opposite error. These concentric masses of lime salt, apparently first described by Gottstein,<sup>24</sup> are very striking when they occur in large numbers, and in no degree discredit a diagnosis of tuberculosis.

A possible source of error is found in the superficial resemblance between a confluent noncaseating tuberculosis and an active diffuse syphilis of the tonsil. The differential diagnosis depends on the relatively avascular character of the former and the arrangement of the epithelioid cells in whorls about minute capillaries in the latter. In confirmation of the diagnosis, specific staining for the organism may be carried out. In our experience, the demonstration of the spirochete in the tonsil is attended with less difficulty than the demonstration of the tubercle bacillus.

33. Austin, R. S.: Bacillus Tuberculosis in the Tonsils of Children Clinically Nontuberculous, *Am. J. Dis. Child.* **18**:15 (July) 1919.

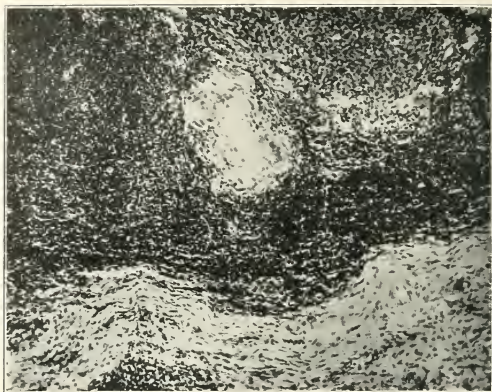


Fig. 1.—Photomicrograph of a foreign body pseudotubercle in the tonsil. The foreign body shows several fine parallel striae, as if composed of a bundle of fibrils, probably vegetable material, and is surrounded by foreign body giant cells. Hemalum and eosin stain, Zeiss "B" objective, without ocular.

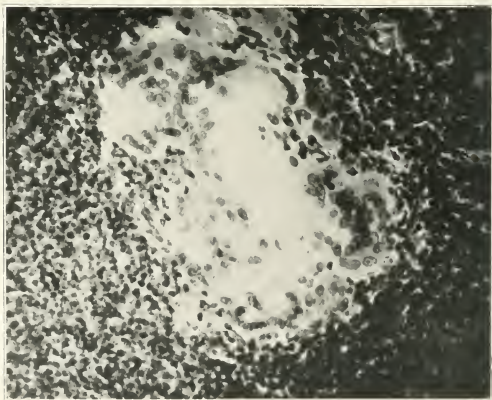


Fig. 2.—Photomicrograph of same foreign body pseudotubercle as in Figure 1. Higher power to show detail of foreign body and giant cells. Zeiss "DD" objective, without ocular.

## THE INCIDENCE OF TONSIL TUBERCULOSIS

The histologic examination of the material removed in 8,697 tonsillectomies, including in practically all cases both faucial tonsils and in many cases both faucial tonsils and adenoids, showed active tuberculosis in 204 instances, a case incidence of 2.35 per cent. This falls within the limits established by other reported series. Taking only those reports which include 100 or more cases, unselected in respect to tuberculosis elsewhere in the body, and omitting several dealing with pharyngeal tonsils only, Table 1 may be constructed.

The aggregate of these previous statistical studies gives a case incidence varying only 0.79 per cent. from our own, although the individual results vary over a wide range.

TABLE 1.—INCIDENCE OF TONSIL TUBERCULOSIS

Author	Cases	Tuberculous	Per Cent.
Albrechts <sup>34</sup> .....	1,000	3	6.3
Barnes <sup>36</sup> .....	150	3	2.0
Crowe, Watkins and Rothholz <sup>37</sup> .....	1,000	46	4.6
Judd <sup>37</sup> .....	1,000	23*	2.3
Lewin <sup>38</sup> .....	300	9	4.5
Robertson <sup>39</sup> .....	232	19 (?)	8.0
Sewall <sup>40</sup> .....	772	30	3.9
Willis <sup>40</sup> .....	108	9	8.0
	4,522	142	3.1

\* Usually quoted as given here, but the report is ambiguous as is shown by the following direct quotation: "In our cases we were seldom able to trace back to the source of entrance. Examinations of several hundred tonsils showed tubercles in much less than 1 per cent. In 1,000 cases, 2.3 per cent. had positive tuberculous lesions."

In Table 2 the distribution of the entire series of 8,697 cases as to age, sex and number of positive and negative cases for each sex at each age is presented.

For purposes of comparison, however, and to avoid as far as possible the error of chance occurrence by increasing the size of the groups, these data will be condensed into five year age periods.

Of the 8,697 cases, there were 8,343 in which information regarding the sex of the patient was available. Of 4,631 tonsillectomies in male patients, 103, or 2.23 per cent., were found to be tuberculous. In 3,712 female patients the tonsils gave histologic evidence of active

34. Albrechts: Quoted by Ravenel.<sup>35</sup>

35. J. A. M. A. **66**:613 (Feb. 26) 1916.

36. Barnes, H. A.: The Tonsils, C. V. Mosby, 1914, p. 160.

37. Judd: Treatment of Tuberculous Glands of the Neck. Ann. Surg. **52**: 758, 1910.

38. Lewin: Ueber Tuberculose der Rachenmandel. Arch. f. Laryngol. u. Rhinol. **9**:377, 1899.

39. Robertson, C. M.: Certain Facts Concerning Faucial Tonsils, J. A. M. A. **47**:1725, 1906.

40. Willis, B. C.: Inflammatory Pathology of the Tonsil, South. M. J. **7**: 747, 1914.

TABLE 2.—INCIDENCE OF TONSIL TUBERCULOSIS AS TO AGE AND SEX

Age	Males		Females		Sex Not Known		Total		Total
	Posi- tive	Nega- tive	Posi- tive	Nega- tive	Posi- tive	Nega- tive	Posi- tive	Nega- tive	
1	...	6	...	3	...	1	...	10	10
2	...	31	...	2	...	...	...	54	56
3	...	94	...	55	...	2	2	151	153
4	...	110	...	68	...	2	...	180	180
5	...	139	...	120	...	3	...	262	262
6	3	170	3	113	...	6	6	280	285
7	...	173	4	136	...	3	4	312	316
8	6	185	4	139	...	4	10	328	338
9	...	152	1	128	...	...	4	260	264
10	...	128	4	109	...	2	6	239	245
11	1	141	3	105	...	3	4	252	256
12	2	120	3	95	...	4	5	219	224
13	3	76	...	117	...	1	3	194	197
14	3	160	3	106	...	...	6	206	212
15	1	86	2	86	...	...	3	172	175
16	3	82	2	89	...	1	5	172	177
17	2	75	6	88	...	...	8	163	171
18	4	131	5	116	...	1	9	251	260
19	4	141	5	115	...	2	9	258	267
20	8	189	3	122	...	2	11	313	324
21	4	160	4	124	...	...	8	323	341
22	3	198	2	88	...	1	5	287	292
23	1	139	5	93	...	1	6	233	239
24	3	157	4	85	...	2	7	244	251
25	2	102	...	57	...	...	2	159	161
26	4	97	2	57	...	...	6	154	160
27	1	49	1	56	...	1	2	106	108
28	4	57	1	42	...	2	5	101	106
29	...	38	1	36	...	...	1	74	75
30	3	36	...	47	...	...	3	83	86
31	1	35	...	23	...	...	1	58	59
32	1	37	2	34	...	1	3	72	75
33	1	27	...	26	...	...	1	53	54
34	1	29	...	15	...	1	1	45	46
35	1	42	2	27	...	...	3	69	72
36	...	26	...	18	...	...	...	44	44
37	...	16	...	17	...	...	...	33	33
38	...	16	1	15	...	1	1	32	33
39	2	19	...	21	...	...	2	27	29
40	...	20	1	8	...	...	1	41	42
41	...	8	1	12	...	...	1	20	21
42	...	10	...	15	...	...	...	25	25
43	...	16	...	14	...	...	...	30	30
44	...	4	2	6	...	...	2	10	12
45	...	8	...	9	...	...	...	17	17
46	...	12	...	10	...	...	...	22	22
47	...	4	...	4	...	...	...	8	8
48	...	6	...	14	...	...	...	20	20
49	...	7	...	8	...	...	...	15	15
50	...	5	...	7	...	...	...	12	12
51	1	5	...	3	...	...	1	8	9
52	...	8	...	8	...	...	...	16	16
53	...	4	...	5	...	...	...	9	9
54	...	3	...	3	...	...	...	6	6
55	...	5	...	3	...	...	...	8	8
56	...	5	...	9	...	...	...	14	14
57	...	3	...	2	...	...	...	5	5
58	1	2	...	2	...	...	1	4	4
59	...	1	1	1	...	...	1	2	3
60	...	3	...	2	...	...	...	5	5
61	...	1	...	1	...	...	...	2	2
62	...	3	...	1	...	...	...	4	4
63	...	4	...	2	...	...	...	6	6
64	...	...	...	3	...	...	...	3	3
65	...	2	...	1	...	...	...	3	3
67	...	1	...	...	...	...	...	1	1
69	...	1	...	...	...	...	...	1	1
70	...	1	...	...	...	...	...	1	1
76	...	...	...	...	...	1	...	1	1
77	...	...	...	1	...	...	...	1	1
78	...	1	...	...	...	...	...	1	1
Not given	20	711	16	648	5	301	43	1,690	1,703
Totals	103	4,528	96	3,616	5	349	204	8,493	8,607



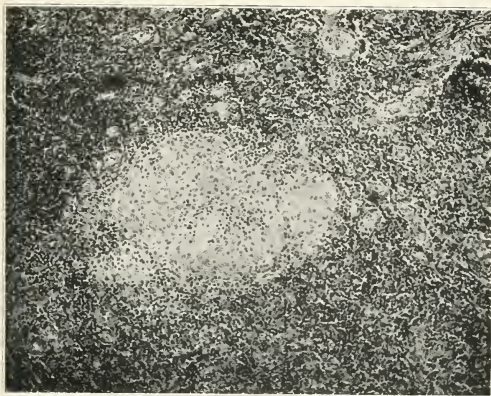


Fig. 3.—Photomicrograph of a tonsil epithelioid tubercle containing a few lymphocytes in its central portion. No caseation. No giant cells. Toluidin blue stain. Zeiss "B" objective, without ocular.



Fig. 4.—Photomicrograph of a tonsil epithelioid, giant cell and lymphocyte tubercle. Very slight caseation. Toluidin blue stain. Zeiss "B" objective, without ocular.



tuberculosis in ninety-six instances, or 2.59 per cent. There is, then, very little difference between the sexes in respect to the incidence of tonsil tuberculosis, but the slightly greater prevalence in females has constantly been present throughout the period covered by this investigation. The distribution of the cases of known age according to sex by five year age periods, as presented in Table 3, shows, also, that at practically all ages this greater incidence in females exists. In one period only, ages 26 to 30, is this condition reversed, and in that instance the total number of cases is not so great but that the discrepancy may have the element of chance occurrence as its sole explanation. The somewhat greater incidence in females of all ages seems, at first glance, to be in contradiction to the general experience for tuberculosis as shown by mortality statistics.<sup>41</sup> In the registration area, and for the year 1917, deaths of females from tuberculosis were 9.9 per cent. of the

TABLE 3.—INCIDENCE OF TONSIL TUBERCULOSIS AS TO FIVE YEAR AGE PERIODS

Age Periods	Males			Females			Sex Unknown		Totals		
	Posi- tive	Nega- tive	Per Cent. Posi- tive	Posi- tive	Nega- tive	Per Cent. Posi- tive	Posi- tive	Nega- tive	Posi- tive	Nega- tive	Per Cent. Posi- tive
1 to 5	2	380	0.53	2	269	0.74	..	8	4	657	0.61
6 to 10	14	808	1.70	16	635	2.56	..	15	30	1,448	2.07
11 to 15	10	526	1.87	11	509	2.12	..	8	21	1,043	1.97
16 to 20	21	621	3.27	21	530	3.81	..	6	42	1,157	3.50
21 to 25	13	805	1.58	15	447	3.25	..	4	28	1,296	2.18
26 to 30	12	279	4.15	5	238	2.06	..	3	17	518	3.18
31 to 35	5	170	2.86	4	125	3.10	..	2	9	297	2.94
36 to 40	2	97	2.02	2	79	2.47	..	1	4	177	2.21
Over 40	2	133	1.48	4	146	2.67	..	1	6	280	2.07

total number of female deaths and deaths of males from tuberculosis were 10.6 per cent. of the total number of male deaths. However, the tonsil cases here considered fall very largely between the ages of 5 and 24 years. Comparing the tuberculosis mortality in these ages with the total mortality of the same period, it is found that female deaths from tuberculosis are 29.2 per cent. of female deaths from all causes and male deaths from tuberculosis 20.9 per cent. of male deaths from all causes. Although it is not altogether safe to substitute mortality statistics for morbidity statistics and to use the number dying at a given age as an index of the number living, it appears, nevertheless, that the greater incidence of tonsillar tuberculosis in females is but part of a general greater incidence of tuberculosis in females during that period of life at which tonsillectomy is most frequently performed.

The youngest cases of tonsillar tuberculosis were found at 2 years of age, two in number, and the oldest case at 59 years. The age incidence by five year periods is shown in the final column of Table 3. It

41. Mortality Statistics, 1917, U. S. Bureau of Census, 1919.



Fig. 5.—Photomicrograph showing confluent epithelioid tubercles beneath the mucosa of a crypt. Lymph follicle uninvolved. Hemalum and eosin stain Zeiss "B," without ocular. Bellow's length 150 cm.



Fig. 6.—Photomicrograph of caseating tuberculous lesion involving the mucosa of a tonsillar crypt. Numerous small epithelioid tubercles beneath the area of caseation. Toluidin blue stain. Zeiss "B," without ocular. Bellow's length 85 cm.

shows an increased incidence after the years of infancy and early childhood have passed. When compared with similar statistics, compiled in 1917 but hitherto unpublished,<sup>42</sup> dealing with this series of cases up to that date, the effect of changes in the constitution of the population considered, is brought out. At that time 4,543 tonsillectomies yielded 138 cases of tuberculosis, a total incidence of slightly over 3 per cent. A comparison of the five year period age incidence at that time with that now obtained is possible in the parallel columns of Table 4. It will be noted that at the time of the earlier compilation the incidence was higher in each age group than at the present time and that this difference was most marked in the very young and in those of adult years. The explanation is probably to be found, in the first place, in the large number of children from certain state institutions who have been sent to the University Hospital for tonsillectomy. The incidence of tonsillar tuberculosis was high in this group (institutional infection) and these patients formed a much greater part of the entire series in the

TABLE 4.—FIVE YEAR AGE PERIOD INCIDENCE IN 1917 AND IN 1920

Age Period	Per Cent. Positive in 1917	Per Cent. Positive in 1920
1 to 5.....	1.4	0.61
6 to 10.....	2.8	2.07
11 to 15.....	2.5	1.97
16 to 20.....	3.9	3.50
21 to 25.....	2.8	2.18
26 to 30.....	5.1	3.18
Over 30.....	5.0	2.46

earlier than in the later years of the period considered. In the second place, the material here considered reflects a changing viewpoint on the part of the otolaryngologist in that an increasing number of patients were operated in the later years in the hope of removing a primary chronic purulent focus. These patients are more especially of adult years and in them the incidence of tonsillar tuberculosis is low. The effect of this group has been to lower the incidence after the age of 25, which had been brought to a high level by reason of the fact that in the earlier years tuberculosis of the cervical nodes or of the lungs was, in a greater proportion of cases, the reason for tonsillectomy in those past the age of excessive lymphoid hyperplasia.

The large number of medical students, interns and nurses who have had unsuspected tuberculosis of the tonsils has been an interesting feature of this investigation. Von Scheibner<sup>30</sup> also noted the frequency of tonsil tuberculosis in nurses. This phase of the incidence of tonsil tuberculosis cannot now be presented by a statistical method.

42. Read at the meeting of the American Association of Pathologists and Bacteriologists, New York. 1917.

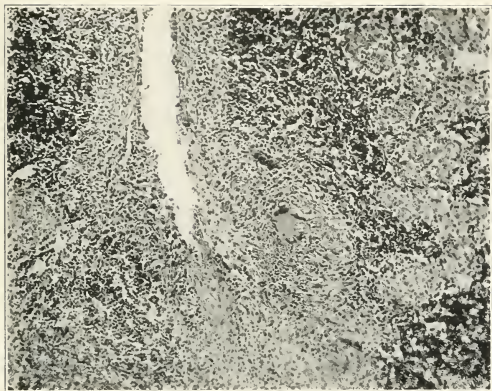


Fig. 7.—Photomicrograph of giant cell and epithelioid tubercles in and beneath the mucosa at the bottom of a crypt. Hemalum and eosin stain. Zeiss "B," without ocular.

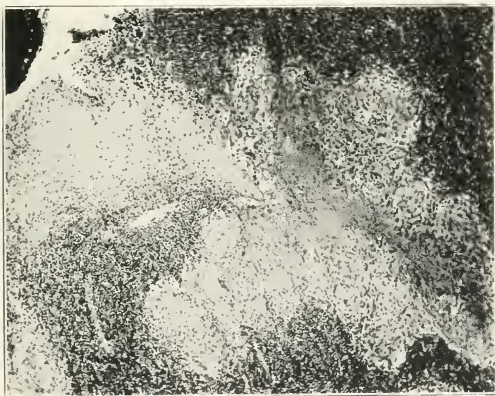


Fig. 8.—Photomicrograph showing submucous confluent epithelioid tubercles with some caseation. Toluidin blue stain. Zeiss "B," without ocular.

but the frequency in these groups has been striking, and can have no other explanation than that most of these cases represent a primary focal tuberculosis.

#### HISTOPATHOLOGY OF TONSILLAR TUBERCULOSIS

The histologic evidences of tuberculosis, as they are met with in the tonsil, differ in no respect from those found elsewhere in lymphadenoid tissue and require no descriptive characterization as far as their recognition is concerned (Figs. 3 and 4). The distribution of the lesions, their location in respect to crypt epithelium and follicles and the various types of tuberculous processes, are the considerations of chief interest.

The tuberculous tonsil is diagnosed clinically but rarely. Except in the very small percentage of cases showing extensive, ulcerative, lupus-like lesions these tonsils show nothing characteristic. The tuberculous

TABLE 5.—DISTRIBUTION OF LESIONS AMONG FAUCIAL AND PHARYNGEAL TONSILS

One Faucial Tonsil	Other Faucial Tonsil	Pharyngeal Tonsil	Number of Cases
Positive	Positive	Positive	2
Positive	Positive	Not examined	44
Positive	Positive	Negative	3
Positive	Not examined	Positive	0
Positive	Negative	Positive	1
Not examined	Not examined	Positive	1
Negative	Negative	Positive	11
Positive	Negative	Not examined	123
Positive	Negative	Negative	9
Positive	Not examined	Not examined	10
Total number of cases.....			204

tonsil may be either hyperplastic or atrophic, prominent or buried. As can be noted in the literature, the inexperienced frequently interpret plugs of caseous debris, expressed from the mouths of the crypts, as gross evidence of caseation necrosis due to tuberculosis. In those cases in which clinical diagnoses of tonsil tuberculosis have been substantiated microscopically, the diagnoses have usually been based on the presence of tuberculous cervical nodes or of pulmonary lesions moderately well advanced, and not on anything manifest in the tonsils themselves.

The coincidence of tuberculosis in both faucial tonsils or in one or both faucial tonsils and pharyngeal tonsil is shown in Table 5. From this table it will be seen that of the 182 positive cases, in which both faucial tonsils could be examined, 133 showed unilateral lesions as compared to forty-nine with bilateral involvement. Of twenty-six positive cases, in which all three tonsils (two faucial and pharyngeal) were examined, the lesions were triple in two cases, double in four cases, and single in twenty cases. These twenty cases consisted of



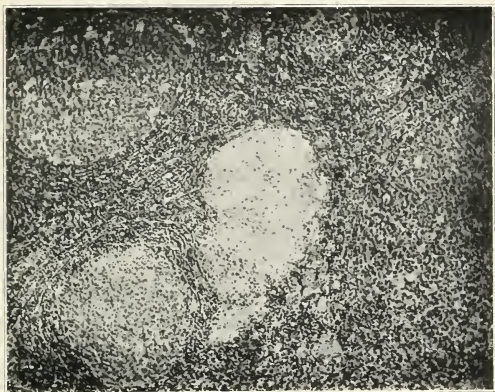


Fig. 9.—Photomicrograph of typical epithelioid tubercle from a crypt infection case. Note noninvolvement of lymph follicles. Toluidin blue stain, Zeiss "B," without ocular.

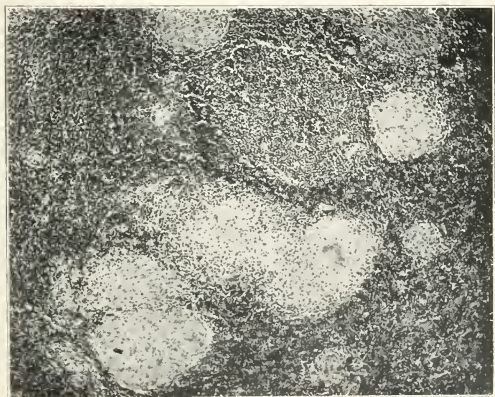


Fig. 10.—Photomicrograph of epithelioid and giant cell tubercles from a crypt infection. Lymph follicles are uninvolved in spite of extensive character of lesion. Toluidin blue stain, Zeiss "B" objective, no ocular.

eleven cases of tuberculosis of adenoids only, and nine cases of tuberculosis of one faucial tonsil only.

The extent of the tuberculous process was gaged by recording the number of tubercles as "many," "few," or "solitary." As measured by this rough scale, 120 cases showed an extensive involvement, fifty-three cases few tubercles only, and thirty-one cases but a single tubercle.

The most common histologic type of tonsil tubercle is the epithelioid tubercle, with or without giant cells (Figs. 5 and 6). Not infrequently numerous very large giant cells occur. Caseation occurs proportionately less frequently than in tuberculosis of the lungs and bronchial nodes. Of the 204 positive cases, only thirty-five showed caseation worthy of note and these were chiefly cases in which the tubercles were sufficiently numerous to be confluent.

The distribution of the lesions within the tonsil is a matter of the greatest importance. Three types may be recognized, and these may occur either alone, or in combination with each other. The first, and most common, is that which may be termed the crypt infection, a manner of distribution which was clearly present in more than 60 per cent. of our cases. The actual incidence of this type is undoubtedly much higher than can be demonstrated, due to the fact that those ramifications of the crypts which occur in the third dimension cannot be appreciated, except by methods of reconstruction from serial sections. In the crypt infection, the tubercles tend to be submucous in position and are confined to the area of one or more crypts (Figs. 7, 8, 9, 10, 11, 15, 17, 18, 19, 20). These crypt areas are often surprisingly extensive. One-fourth or one-third of a tonsil may be tuberculous, and yet a careful tracing of the crypts in that area will show that they have a common mouth. The slitlike character of the crypts likewise increases the apparent extent of the area involved from a single crypt, for the lateral extensions are rarely borne in mind. The more important connective tissue septums serve to define the areas of individual or closely related crypts and groups of lesions bounded by such septa may be assumed to have a common origin. In this type of tonsillar tuberculosis the lymph follicles are involved not at all or only late in the process and the lesions are very frequently unilateral.

As by far the most common type of tonsil tuberculosis, the "crypt infection," with its localized lesions, sub-mucous tubercles and usual failure to involve the lymph follicles, has been the form described by most authors. Piffi<sup>16</sup> noted the submucous position of the tubercles in adenoid tuberculosis. Robertson<sup>39</sup> designated three or four crypts, emptying into the supratonsillar fossa as "the infecting crypts of the tonsil." Mitchell<sup>28</sup> found that tuberculous lesions occurred in three

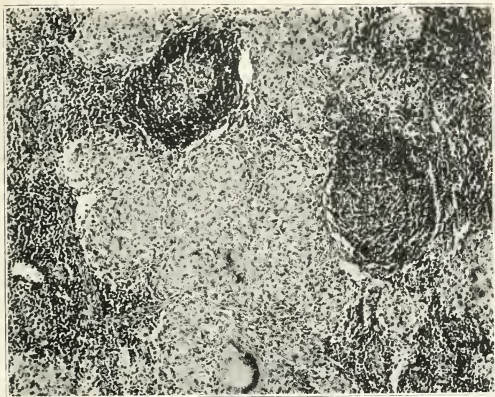


Fig. 11.—Photomicrograph showing extensive tonsillar tuberculosis. Crypt infection type. Lymph follicles remain uninvolved. Hemalum and eosin stain. Zeiss objective "B," no ocular, bellows length, 150 cm.

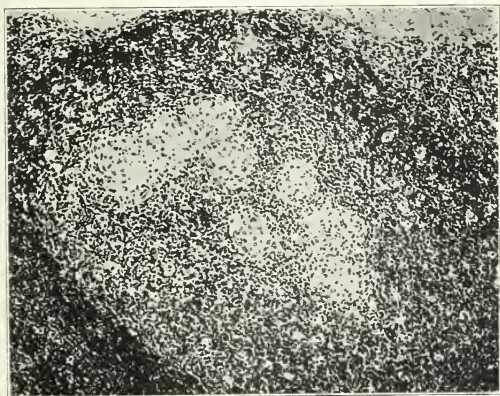


Fig. 12.—Photomicrograph showing epithelioid miliary tubercles in lymph follicle of tonsil. Diffuse miliary tonsillar tuberculosis. Toluidin blue stain. Zeiss objective "B," no ocular.



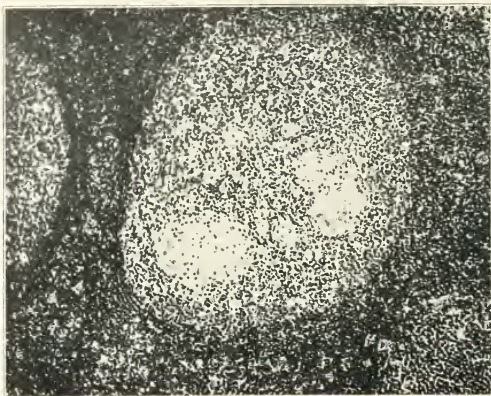


Fig. 13.—Photomicrograph showing epithelioid miliary tubercles in lymph follicle of tonsil. Diffuse miliary tonsillar tuberculosis. Toluidin blue stain. Zeiss objective "B," no ocular.

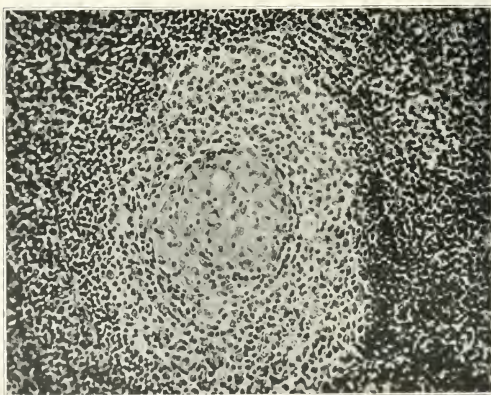


Fig. 14.—Photomicrograph showing epithelioid miliary tubercle in germ center of follicle. Note formation of tubercle about wall of arteriole of the follicle. Diffuse hematogenous miliary tuberculosis. Toluidin blue stain. Zeiss "11D," no ocular.



Fig. 15.—Right and left tonsils from Case 1294-U. Tracings of vertical sections made by direct projection through 48 mm. objective. Solid black indicates areas of tuberculosis; the open circles, the more prominent follicles. Tuberculosis confined to a single crypt area of one tonsil only. Crypt infection, limited by septum. Follicles not involved.

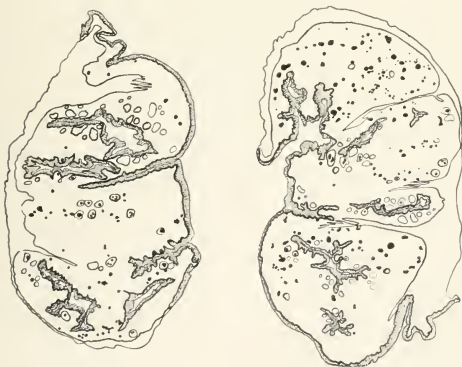


Fig. 16.—Tracings of right and left tonsils of Case 3832-U. The tubercles are shown in solid black and are found to be nearly uniformly distributed throughout both tonsils. Their location is not determined by crypts or septa and many are found in follicles. Hematogenous miliary tuberculosis.

situations: surrounding the deeper parts of the crypts, especially the supratonsillar group; immediately under the mucous membrane near the mouths of the crypts; and deep in the tonsil, close to the posterior capsule. At the bottom of the crypts, near the capsular surface, was the most common location as found by Crowe, Watkins and Rothholz.<sup>20</sup>

The second group of cases includes those which are recognized as tuberculous by their gross appearances—the ulcerative lupuslike lesions. These result from extensive, coalescing, multiple crypt infections such as may be found in the massive auto-infections of the tonsil in some open cases of pulmonary tuberculosis, or from involvement of the tonsil in an ulcerative tuberculosis of mouth or pharynx.

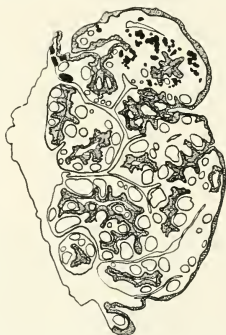


Fig. 17.—Tracing showing areas of tuberculosis (solid black), crypt systems and prominent follicles in one tonsil of Case 583-P. A crypt infection. Other tonsil not involved.

The third type of tonsil tuberculosis is one which has not, to our knowledge, been described previously, and the significance of which has not hitherto been established. In this form, the lesions are usually bilateral, are widely scattered throughout the tonsil rather than grouped in crypt areas, and characteristically involve the lymph follicles and even the germ centers of the follicles (Figs. 12, 13, 14, 16). It is, therefore, in these three particulars, in sharp contrast to the form described in the first group. The occurrence of tubercles within the germ centers gives a picture strikingly unlike the usual tonsillar tuberculosis. Cases are met with in which the tubercles, even though very numerous throughout the sections, are found in no other location.

Observations of tubercles so situated have been recorded occasionally in the literature. Pluder and Fischer<sup>13</sup> found in one of their cases of adenoid tuberculosis that the tubercles were situated partly within and partly between the follicles. In one of his cases, also, Ruge<sup>43</sup> described the tubercles as occurring singly and chiefly within the follicles. In Gottstein's<sup>23</sup> Case 3 almost the entire section of pharyngeal tonsil was involved and there were numerous tubercles in the follicles. In his Case 5 there were tubercles in the follicles of both adenoids and tonsils, and in Case 6 some follicles contained small tubercles with giant cells. These authors, however, do not consider these cases as belonging to a distinct group.



Fig. 18.—A sharply localized crypt infection in one tonsil of Case 639-O. Other tonsil free.

We have had sixteen cases of tonsil tuberculosis with the tubercles occurring chiefly or exclusively in the germ centers. Of these, nine showed bilateral lesions and of the other seven, there were three in which only a single follicle was involved, and hence the unilateral character was without significance. There were only two instances in which the pharyngeal tonsil was also examined. In one of these, all three tonsils showed a diffuse follicular distribution while the other case was one of those in which one follicle only was involved.

It is our belief that an important clinical significance attaches to the recognition of the type of tonsil tuberculosis. The "crypt area" infections, submucous, usually unilateral and involving the follicles very late, if at all, are focal processes, infections from without, either primary or autoinfections. The scattered lesions, usually bilateral and occurring chiefly in the follicles, are the result of a hematogenous dissemination of tubercle bacilli. When this is borne in mind, it will be seen that many mixed cases will occur. These should be found particularly in those patients who have advanced pulmonary tuberculosis with



Fig. 19.—Case 1495-V. Tonsillar tuberculosis involving one tonsil only. On casual examination lesions might seem to be quite widely scattered, but the tracing shows that they are confined to a single crypt area. They do not involve the follicles.

sputum rich in organisms, and who suffer at the same time from general miliary dissemination. This is found to hold true in cases of tonsillar tuberculosis which we have studied postmortem (a class of material not included in the statistical analysis given here). Tonsils from such patients usually show one or more definite areas of crypt infection and a miliary tuberculosis of the follicles comparable in degree

to the miliary dissemination in other organs, such as liver, spleen and kidneys. These points will receive further consideration in the general discussion which follows.

#### DISCUSSION

It is not within the scope of this paper to attempt to make a case by case comparison of the histopathologic changes in the tonsil with the clinical data. There are, however, certain clinical considerations which must be given further explanation.

It has already been pointed out that from the limitations of the method employed, the incidence of tonsil tuberculosis, here shown to



Fig. 20.—Case 1500-S. Tracing showing in solid black the distribution of tubercles in a case with apparently multiple crypt infections. Follicles (open circles) are not involved in the tuberculous process.

be 2.35 per cent., is of necessity lower than the actual incidence by an unknown amount. It must be emphasized, also, that this incidence is one of active lesions only. Hyalin scars, areas of fibrosis, more or less rounded in outline and poor in blood vessels, are frequently met with in tonsils showing no active lesions. It is probable that most of these areas are healed or healing tubercles. They cannot be differentiated from the older tubercles in tonsils showing miliary tubercles of all ages. It is our opinion that with all the healed lesions included and all por-

tions of the tonsil systematically examined, tonsillar tuberculosis would be found to be as universal as is pleural and pulmonary tuberculosis. The solitary tubercles, occurrence of which, in an active stage, was noted in thirty-one of our 204 cases, in general have no further significance than that they are a part of this universal infection, their discovery being purely accidental. In some instances they may indicate the dissemination of a limited number of bacilli with the production of but few miliary tubercles.

The preponderance of epithelioid and giant cell tubercles over caseating lesions in tonsillar tuberculosis suggests that the type of the infecting organism is not infrequently one of only moderate virulence. The histologic character of the lesions, determined by the balance between the necrosing agent and the reparative activity of the tissues, in many cases points to the bovine rather than the human type of tubercle bacillus as the infecting agent. Judgment on this point is of necessity uncertain and cannot go much beyond a general impression, but the results of bacteriological examination of tuberculous tonsils and cervical nodes prove of interest in this connection. Mitchell<sup>22</sup> identified the strain in twenty-six cases of tonsil tuberculosis in children and found twenty to be bovine and six human. In seventy-two consecutive cases of tuberculous cervical nodes the same author<sup>28</sup> found sixty-five bovine and seven human. Park and Krumwiede<sup>43a</sup> found the same preponderance of the bovine strain in cervical node tuberculosis in young children while in older children the human strain became the more common. Under 5 years, they found six human and twelve bovine; between 5 and 16 years, nineteen human and eight bovine; 16 years and over, nine human, no bovine. In a large series of tuberculous cervical nodes, Griffith<sup>44</sup> found the proportion of bovine infection to decrease regularly from 85.7 per cent. under 5 years of age to 19.0 per cent. at 20 years and over. It seems reasonable, therefore, to attribute the relative freedom from caseation to the bovine strain of organism as the more common invader, particularly in the tonsils of young children.

The crypt infection type of tonsillar tuberculosis can be explained only on the basis of the entrance of the infection from the mucosal side and not by the hematogenous or lymphogenous routes. The characteristic unilateral, or better, monotonsillar, involvement, the limited localization of the process within the affected tonsil, the frequent sub-

43. Ruge: Die Tuberculose der Tonsillen vom klinischen Standpunkte, Arch. f. path. Anat. u. Physiol. **144**:431, 1896.

43a. Park and Krumwiede. The Relative Importance of the Bovine and Human Types of Tubercle Bacilli in the Different Forms of Human Tuberculosis, J. M. Research **23**:205, 1910.

44. Griffith, A. S.: Types of Tubercle Bacilli in Cervical and Axillary Gland Tuberculosis, Lancet **1**:216, 1917.

mucous position of the tubercles and the avoidance of the follicles all point to mucosal infection. This may, of course, be either a primary infection or a secondary, that is, autoinfection. We can be certain that both occur in our series. Those cases in which the crypt infection is not monotonsillar, but double or triple, are usually, but not necessarily, cases of autoinfection and should be examined carefully for open lesions elsewhere in the respiratory tract. A majority of the monotonsillar and some of the double and triple crypt infections are primary tonsil tuberculosis. These are the patients who show no evidence of active tuberculosis elsewhere in the body and in their subsequent history often show no evolution of the disease. It must be emphasized that the absence of clinical evidence of active tuberculosis elsewhere in the body would have little value if we had not previously established the fact that the type of infection of which we are now speaking comes through the mucosa. It requires an open lesion for the crypt type of auto-infection and clinical evidence should be forthcoming either before or after the occurrence of tonsillar invasion. The monotonsillar crypt infection has been very common in nurses, interns and upper class medical students. Many of these cases have been followed up and have shown no further lesions. We are convinced that most of these cases are examples of primary focal tonsil tuberculosis. The infectious material is either inspired or ingested. Experimental evidence of the possibility of tonsillar infection in this manner is abundant. Feeding experiments with infected material, such as were carried out by Orth,<sup>45</sup> Baumgarten<sup>45</sup> and others, and the infusion of lamp black into the pharynx by Hendelsohn<sup>46</sup> and injection of carmin into the tonsillar crypts by Goodale<sup>47</sup> have all shown that both living organisms and inert particles present in the pharynx and tonsillar crypts pass into the tonsil with ease.

On the other hand, the third type of tonsil tuberculosis, the diffuse follicular miliary tuberculosis, in all of its characteristics points to a hematogenous origin, the terminals of the follicular arterioles being the seat of lodgment of the bacilli. If this process were frequently unilateral, a retrograde lymphogenous metastasis from the cervical nodes might be considered, especially in view of the work of Blum<sup>48</sup> who reported that both inert substances and living organisms injected into the cervical nodes of guinea-pigs were subsequently found in the

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45. Baumgarten: Ueber die Uebertragbarkeit der Tuberculose durch die Nahrung, *Centralbl. f. klin. Med.* **5**:25, 1884.

46. Hendelsohn: Ueber das Verhalten des Mandelgewebes gegen aufblasene pulverförmige Substanzen, *Arch. f. Laryngol. u. Rhinol.* **8**:476, 1898.

47. Goodale: Absorption von Fremdkörpern durch die Gaumentonsillen, *Arch. f. Laryngol.* **7**:90, 1898.

48. Blum, S.: Tonsils Excretory Organs for Cervical Glands: Preliminary Report, *Arch. Pediat.* **32**:837, 1915.



tonsils and in the oral cavity. Such a retrograde metastasis in the slowly moving lymph stream, subjected to the irregular pressures produced by the contraction of nearby muscles, is to be expected. But the type of tonsil tuberculosis in which the tubercles occur chiefly in the follicles is usually bilateral and frequently universal in its involvement of the tonsils. The work of Goodale<sup>47</sup> and of Hendelsohn<sup>48</sup> has an application here not anticipated by those investigators. The former found that carmin particles injected into the tonsillar crypts penetrated all other portions of the tonsil more promptly than the follicles. In tonsils removed up to two hours after injection none was found in the interior of the follicles. Even at five and ten days, although the interfollicular lymph spaces contain much carmin the interior of the follicles showed none and there was but little in the neighborhood of the germ centers. Hendelsohn<sup>48</sup> found that only with more intense applications of dust to the tonsil were any particles found within the follicles and he notes the analogy between his observation and that of Arnold<sup>49</sup> who found that the follicles and germ centers of lymph nodes remain relatively free even when the interfollicular tissue is loaded with dust.

It is not within the scope of this paper to enter at length into a discussion of the relationship of tonsillar to cervical gland and pulmonary tuberculosis. Our cases include many in which cervical nodes were examined histologically after the tonsils were found to be tuberculous. In some of these the nodes were also found to be tuberculous. In other cases, extensive tonsillar tuberculosis was unaccompanied by cervical gland lesions. The converse was even more frequently noted, the tonsils from patients with extensive cervical node lesions failing to show any lesions. Nevertheless, the tonsil must be considered the most important portal of entrance in cervical gland tuberculosis.

The relationship to pleural and pulmonary tuberculosis is even more difficult to analyze. The work of Grober<sup>24</sup> in tracing carbon particles injected into the tonsils to the pleura and pleural space by way of the cervical lymphatics is much quoted. Van Zwaluwenburg and Grabfield<sup>50</sup> find that patients with tonsillar tuberculosis almost invariably show, in stereograms of the thorax, changes in the apical pleura which they believe are due to tuberculosis. However, we have failed to find tuberculosis in the tonsils removed from a number of such cases.

From the pathologist's standpoint, an incidence of active tonsillar tuberculosis of more than 2.35 per cent, should not, in itself, be consid-

49. Arnold: Untersuchungen über Staubinhalation und Staubmetastase. Leipzig, 1885.

50. Van Zwaluwenburg and Grabfield: Papers now in press, to appear in American Review of Tuberculosis, 1921, and to which I am permitted to refer through the kindness of the senior author.

ered an argument for tonsillectomy. The facts here presented, however, do lead to the belief that it is advisable to remove the tonsils in cases of known cervical nodes or pulmonary tuberculosis in the hope of removing an active focus of dissemination.

#### CONCLUSIONS

1. The systematic search of a limited number of microscopic sections, so oriented as to show in each the entire surface of a vertically bisected tonsil, is the only practicable routine method for detecting tonsil tuberculosis.

2. The incidence of active tonsil tuberculosis in a series of 8,697 consecutive cases was found to be 2.35 per cent. This minimum figure would have been increased by an unknown, but probably small, amount if it had been possible to examine all portions of each tonsil.

3. The incidence in respect to sex shows tonsil tuberculosis to be slightly more common in females than in males at practically all ages.

4. In the series of 204 positive cases here reported, the range of ages was from 2 to 59 years. The incidence in various age groups depends largely on the character of the population from which the material is derived, the incidence being particularly high in institutions for the care of children and among medical students, interns and nurses.

5. Tonsil tuberculosis may be divided into three types: focal crypt infections; ulcerative lupus-like lesions; and diffuse miliary tuberculosis.

6. The crypt infection is the most common type, is usually unilateral, involves one or more crypt areas only and avoids the lymph follicles. Some of these cases are autoinfections in open respiratory tract tuberculosis but the majority must be considered cases of primary focal tonsil tuberculosis.

7. The ulcerative lupus-like lesions result from the coalescence of crypt infections at the mouths of crypts or from direct extension from neighboring surfaces.

8. The diffuse miliary tuberculosis is usually a bilateral or, if the pharyngeal tonsil is examined, a universal tonsil lesion. The tubercles are widely scattered and occur almost exclusively in the follicles and germ centers. This type can best be explained as a hematogenous miliary dissemination.

9. Mixed types occur, as in patients with open pulmonary tuberculosis, in which autoinfection may be associated with hematogenous miliary tuberculosis giving a combination of crypt infections with diffuse miliary tubercles.<sup>51</sup>

51. The following references will also be found to have bearing on the subject of tonsil tuberculosis:

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The original pathologic diagnoses of the greater part of the material on which this study is based were made by Dr. A. S. Warthin. To him I acknowledge my indebtedness for the use of this material, as well as for many helpful suggestions throughout the prosecution of the work.

## FATAL CHRONIC NEPHRITIS IN A FOURTEEN YEAR OLD GIRL WITH ONLY ONE KIDNEY AND A HISTORY OF SCARLET FEVER\*

O. H. PERRY PEPPER, M.D., AND BALDWIN LUCKE, M.D.

PHILADELPHIA

The recognition of the factors which in a given individual have led to the development of chronic nephritis, is both difficult and important. The whole problem of the etiology of chronic nephritis is inherently confused by the variety of possible contributing causes and by the long interval which usually intervenes before the symptomatic stage of the disease appears. For this reason cases which seem to present new aspects of this problem deserve to be studied carefully and recorded, even though alone they do not justify far reaching conclusions. Such a case is the basis of this report. In this instance two distinct etiologic factors are present; the renal anomaly and the occurrence of a severe attack of scarlet fever. Death resulted apparently as a direct result of one or both of these factors at a sufficiently early age to exclude the action of many of the contributing causes of chronic nephritis which complicate the study of adult cases. This fact makes the study of this case of peculiar interest, and especially as the clinical picture was identical with that of the chronic nephritis of adult life.

The question of the influence that the aplasia of one kidney may have on the functional capacity and susceptibility to disease of the other kidney has received some attention, likewise the broader question of the influence of any renal anomaly on renal function. Thus Babes,<sup>1</sup> Anders<sup>2</sup> and Coplin,<sup>3</sup> have each presented evidence on different aspects of this subject, which will be referred to later. A number of case reports also are available but none presents the same points of interest as the case which is the basis of this paper. Concerning scarlet fever as a possible cause of chronic nephritis, the literature is extensive but inconclusive.

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\*From the Medical Clinic of the Hospital of the University of Pennsylvania, and the McManes Laboratory of Pathology of the University of Pennsylvania.

1. Babes, V.: *La néphrite hypogénétique*, *Semaine méd.* **25**:63 (Feb. 8) 1905.

2. Anders, J. M.: *Congenital Single Kidney*, *Am. J. M. Sc.* **139**:313 (March) 1910.

3. Coplin, W. M. L.: *Unilateral Renal Hypoplasia and Dysplasia Due to Defective Arteriogenesis; Relation to So-Called Hypogenetic Nephritis*, *Am. J. M. Sc.* **153**:381 (March) 1917.

## REPORT OF CASE

F. M. B., aged 14, admitted to the Hospital of the University of Pennsylvania on the service of Prof. Alfred Stengel, March 8, 1920.

*Previous History.*—The girl's family gave the history that she had never been strong since an attack of scarlet fever at the age of 7. This attack was severe but no history of kidney involvement or edema could be elicited. Since the scarlet fever she had had occasional attacks of belching and vomiting which were more severe for the past two months. Jan. 15, 1920, a little less than two months before admission, she had an attack of marked blurring of vision and loss of power in her left arm and both legs. Touch sensation was said to have been abolished, and there was some difficulty with speech and swallowing. Within twenty-four hours the difficulty with speech had disappeared; three days later her sight cleared up, and within two weeks the power in the limbs had returned. About two weeks before admission she had an acute attack ushered in by profuse vomiting, which was diagnosed as "grippe."



Fig. 1.—The right (single) kidney of the patient. The organ weighs 65 gm., is much deformed, and very sclerotic. Note the tumor-like projections at either end of the upper border; there are adenomatous-like masses of newly formed renal tubules.

Her menses first appeared at the age of 12, and at first were exceedingly free; later they became less so but were accompanied each month by bleeding from the nose. The epistaxis sometimes occurred during the interval between the periods as well. The last menstrual bleeding commenced February 28, nine days before admission and continued until admission. Nosebleed appeared with the menses as usual and March 4 became so profuse as to require packing. The nose was repacked March 6. March 7 the gums began to bleed freely. She was admitted March 8 in a very much weakened state. The previous medical history includes in addition to the scarlet fever, pneumonia at the age of 2, typhoid fever at the age of 3, and mumps at the age of 4. The social and family history is negative.

*Physical Examination.*—The patient was an acutely ill young girl who did not look her stated age. She was pallid, pasty and puffy; eye grounds normal, except for slight clouding of disk margins. The breath had a markedly urinous odor. Nares showed evidence of recent epistaxis. The lips were crusted with blood, and the gums bled at the slightest touch. The lungs were negative. The heart was negative, except for accentuated second sounds at the base. Blood pressure: systolic, 148; diastolic, 132. Abdomen negative. No peripheral edema. Reflexes all present.

*Laboratory Examinations.*—Urine (catheterized): clear; lemon color; sp. gr., 1.008; albumin, faint trace; sugar, negative. Microscopic: Casts, negative; cylindroids, negative; erythrocytes, few to each high power field; leukocytes, from 4 to 6 to each high power field.

Blood: Red blood cells, 2,270,000; white blood cells, 5,300; hemoglobin, 50 per cent.; platelets, 220,800. Differential count of white cells: normal. Blood

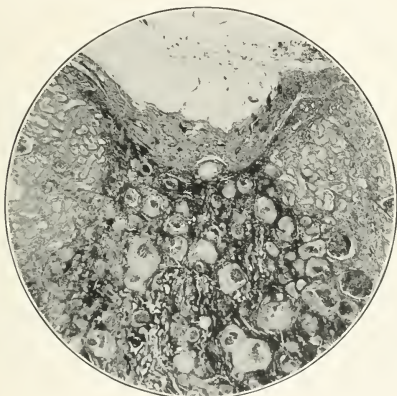


Fig. 2.—A retracted, dense, wedge shaped portion of the renal cortex with the thickened capsule. This area contains massed glomeruli, many of which are much enlarged and possess greatly thickened Bowman's capsules; between the glomeruli lies a richly cellular scar tissue. On either side of this dense region are granulations made up chiefly of newly formed tubules. ( $\times 23$ .)

urea nitrogen: 210 mg. per 100 c.c. Blood plasma carbon dioxide: 29 volumes per cent.

The following day the blood pressure was: systolic, 140; diastolic, 105. There was little change in her condition.

March 11: Some tremor of left eyelid and convulsive movements of left hand were noted. Urine showed little change. Blood pressure: systolic, 120; diastolic, 60.

Phenolsulphonephthalein test: no elimination of dye in two hours.

Blood urea nitrogen: 228 mg. per 100 c.c.

Blood plasma carbon dioxide: 50 volumes per cent.

Blood count: Red blood cells, 2,250,000; white blood cells, 13,400; hemoglobin, 36 per cent. Differential: Neutrophils, 88 per cent.; small lymphocytes, 8 per cent.; large lymphocytes, 2 per cent.; transitionals, 2 per cent.

March 12: Patient steadily grew worse and died. Throughout her course there was a little fever; the pulse rate and respiratory rate were variable and above normal.

#### PATHOLOGIC REPORT

Since only the renal condition has any bearing on this study, the protocol is summarized as follows:

*Necropsy Protocol* (6435).—Anatomic diagnosis: early general arteriosclerosis, slight congestion and edema of lungs; slight fibrosis of spleen; submucous hemorrhages of intestines; cloudy swelling of liver; slight cardiac hypertrophy (230 gm.; body weight, 55 kg.). Aplasia of left kidney and its ureter. Histologic study of tissue removed from the usual site of the left

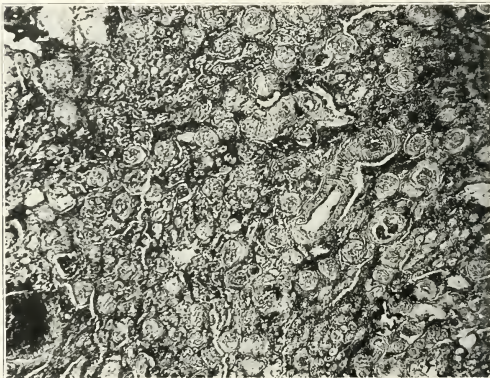


Fig. 3.—Thickly massed, more or less hyalinized glomeruli are surrounded by small round cells (lymphocytes) and richly cellular connective tissues. Tubules are practically absent. ( $\times 50$ .)

kidney did not disclose any kidney anlage. Microscopic examination of the various organs confirmed the gross diagnosis.

**Right Kidney:** The right kidney weighs 65 gm., measures 7 by 4.5 by 3 cm. and has a somewhat trapezoid shape (Fig. 1). The organ is very tough, its capsule adheres firmly to the pale reddish-gray, very irregular surface. Several paler coarse, tumor-like knobs project from 5 to 8 mm. above the general surface, especially near the convexity of the organ. Between these masses the surface appears finely granular and depressed. The capsule is much more adherent to the depressed than to the projected regions; the consistency of the latter is but little greater than normal kidney substance, while the intervening tissue is very firm. The cut surface is even; the projecting nodules seem to be somewhat altered renal lobules, for a thin cortical zone, which averages 2 mm., can be more or less well distinguished from the medulla. The

detailed architecture, however, is disturbed, for while here and there glomeruli and cortical striations stand out prominently they cannot be recognized in other portions. In the depressed areas the corticomedullary differentiation is generally lost. In the outer region the tissue has a pale gray appearance with here and there some reddish dots and lines. The cut vessels appear slightly stiffened, the medullary striations are very indistinct. The pelvic mucosa is pale and appears somewhat thickened. The ureter appears grossly normal. The renal artery is somewhat stiffened, and near its origin the intima shows yellowish, slightly raised patches. The urinary bladder contains only one ureteral opening.

Sections of the kidney were fixed in Orth's fluid and in 5 per cent. liquor formaldehyd. Paraffin sections were stained with eosin-hematoxylin, by Van Gieson's method, and with Weigert's elastica stain.



Fig. 4.—The glomeruli are almost entirely fibrosed or hyalinized. In some nuclear remnants may still be seen. The degenerated tufts are usually fused with the thickened and hyalinized capsules. ( $\times 165$ .)

*Microscopic Description.*—The general architecture is so greatly altered that in many regions the tissue bears no resemblance to renal substance. The cortical outline is coarsely uneven; irregular, richly cellular patches of scar tissue, many with hyalinized glomeruli, alternate with islands or projections of widely dilated tubules, while elsewhere a more diffuse connective overgrowth surrounds variously altered tubules and glomeruli. The capsule is thickened from two to six times its average width, and has a lamellar arrangement. It consists of fibrillar, partly hyalinized connective tissue in which fairly numerous thin walled dilated blood vessels are found. The thicker portions of the capsule occur at points where the cortical periphery is retracted, the thinner portions cover cortical granulations. The cortical periphery is irregular and



wavy, shallow retractions alternating with projections. Broad wedges or thin, streaky patches extend from the indented cortex to within the medullary region (Fig. 2). These areas are made up of densely packed small, round cells, which have a deep staining, compact nucleus and very little cytoplasm, and which correspond to cells of the lymphocyte series. Within such cellular masses there are thickly massed more or less destroyed glomeruli, many collapsed and atrophic tubules, and occasional normal sized or dilated tubules. Besides the lymphatic cells slightly larger elements with somewhat elongated nuclei occur; these are young connective tissue cells (Fig. 3). The supporting fibrous tissue is difficult to see here because of the close, cellular grouping, but is rendered very prominent with Van Gieson's stain. The thickly massed glomeruli are generally of normal size, sharply circumscribed and almost entirely fibrosed or hyalinized.

Many, however, still retain some structural details. Each of these glomeruli usually possesses a small, collapsed, bloodless tuft, adherent to an enormously thickened capsule. The capsules invariably are partly or wholly hyalinized,

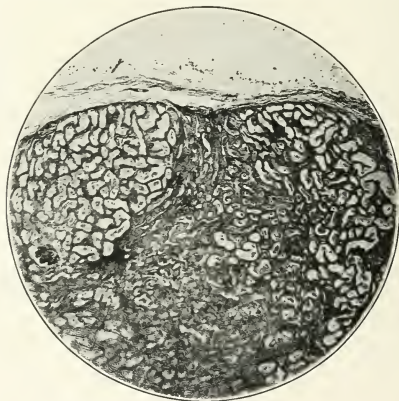


Fig. 5. Two adenomatous-like projections composed of newly formed tubules. Note the large size and irregular shape of the tubules. ( $\times 23$ .)

and either possess no cellular lining or their epithelium is flattened, or occasional swollen cells are present. Proliferation of the lining epithelium is nowhere found (this does not exclude the possibility of such having occurred at a former period) (Fig. 4). Many vasa afferentia and vasa efferentia lie in the neighborhood of the glomerular colonies. These vessels present practically always a moderate but distinct thickening and hyalinization of the sub-endothelial intima. Splitting of the internal elastic and increase of elastic fibers is usually well brought out with Weigert's stain. In no instance, however, is there any decided narrowing of the vascular lumen. The entire region has a poor capillary blood supply; the vessels are nowhere engorged; many are collapsed and difficult to recognize. Normal tubules are absent in the

cellular regions. Those present are often widely separated from their neighbors by the cellular connective tissue and the lymphatic elements. They often are shrunken and collapsed; and can only be recognized because of their paler and larger nuclei. Sometimes they possess peculiar deep staining lining cells, and occasionally an indistinct mitotic figure is encountered. Most of the tubules are filled with a smooth eosin-staining hyalin material. In the outer zone of the medulla the straight tubules are embedded in the same fibrocellular proliferation and infiltration; they likewise are completely filled with hyalin material.

The cortical projections consist of tubular masses, having a peculiar structure. These projections are often round or oval and more or less isolated by dense fibrocellular tissue. Such tubular groups bear considerable resemblance to an adenoma (Fig. 5). This is due to the bizarre structure of the component tubules which are often of great size, branched, serpentine shaped, or show



Fig. 6.—Greatly dilated, bizarre shaped tubules containing granular debris. Glomeruli are absent in this region. ( $\times 70$ .)

infolding of the lining epithelium (Fig. 6). But few have normal oval or round shape. The lining is likewise unlike that of any portion of the normal tubules. The cells are generally large, cuboidal or low columnar, possessing eosin-staining cytoplasm and prominent basal nuclei (Fig. 7). The cellular outline is nowhere very sharp, but is better defined than that of the normal convoluted tubules, but not as clear as in the normal collecting tubules. The cells are generally well preserved, but with Van Gieson's stain fine hyalin-like droplets may be seen in many.

Some tubules possess a very different lining; the cells are usually somewhat smaller, the cytoplasm has a faint bluish tint, the nuclei are large and take a deep stain. In other tubules syncytial cell masses are seen, and now and then a mitotic figure. The wide tubular lumen usually contains some eosin staining debris, much of which is in the form of round droplets of somewhat

larger size and paler color than erythrocytes. The intertubular connective tissue is quite distinct and more or less cellular. Many of the infolded tubules which possess syncytial cell linings roughly resemble fetal glomeruli. Indeed most of the tubules appear more like fetal than adult structures. Very few glomeruli are present in the tubular knobs. Smaller groups of similar tubules are scattered here and there throughout the scar tissue.

Adjacent and subjacent to the richly cellular patches and the adenoma-like tubular projections and foci described, the rest of the renal tissue is seen to be likewise greatly altered (Fig. 8). The intertubular connective tissue is irregularly and considerably increased, its character being partly adult, partly young and fibroblastic. The tubules are either collapsed or dilated or of the same bizarre makeup as detailed above. Normal tubules are nowhere seen. Regenerative features here as elsewhere are common; thus one finds fetal types of newly formed branching tubules; relined old tubules with promi-

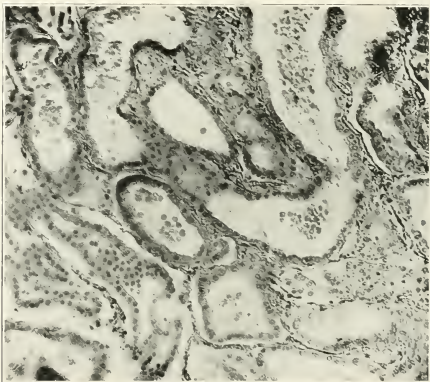


Fig. 7.—Newly formed, morphologically and functionally insufficient tubules, lined with cuboidal or low columnar cells, which are poorly differentiated. The tubular lumina contain round eosin staining hyalin bodies. ( $\times 165$ .)

nently staining cells and occasional mitotic figures, or hypertrophic tubules. The glomeruli are few in number but of enormous size. Many have a diameter up to 370 microns (Fig. 9). Their capsules are always somewhat thickened; the capsular endothelium is generally flattened or at most slightly swollen. proliferation of the epithelium is nowhere seen (Fig. 10). The glomerular tufts are richly nuclear, the nuclei seemingly being of endothelial type, although this cannot be determined definitely. Many capillary loops appear collapsed, others are moderately engorged. On the whole, the glomerular loops contain less blood than normally. No foreign cells are seen within the capillaries.

The medulla appears quite as much involved as the cortex. The tissue is everywhere fibrosed, the type of connective tissue proliferation being the same as in the cortex. Lymphocytic cells are plentiful in some areas, while else-

where denser connective tissue separates dilated or collapsed tubules. No tubules possess a lining resembling that of normal collecting tubules. Many have lost their lining cells and are filled with granular or cellular debris.

When we sum up the anatomic alterations in this case we find that we deal here (a) with an aplasia of one kidney, and (b) with a greatly scarred and atrophic remaining kidney, which histologically answers to the description of "genuine" contracted kidney (true chronic interstitial nephritis). Since the terminology of renal disease is so involved it may be well to state that we are in accord with Aschoff's<sup>4</sup> conception

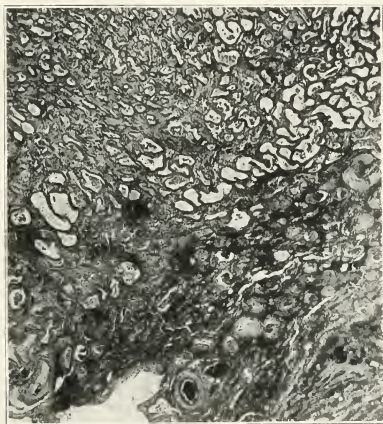


Fig. 8.—A deeper portion of the cortex showing a very dense fibrocellular region adjacent to dilated, hypertrophic tubules, many of which are newly formed, and small collapsed tubules. (About  $\times 50$ .)

of this type of nephritis. A comparison of our photographs with Figure 329 in the second volume of his fourth edition will illustrate rather better than words the striking similarity.

The remarkable degree of regeneration in this kidney must be emphasized. Practically all the tubules are either relined, or entirely reformed. Such new formed tubules are quite commonly found in focal disease of the kidney; they are morphologically and functionally

4. Aschoff, L.: *Pathologische Anatomie*, Ed. 4, G. Fischer, Jena, 1919

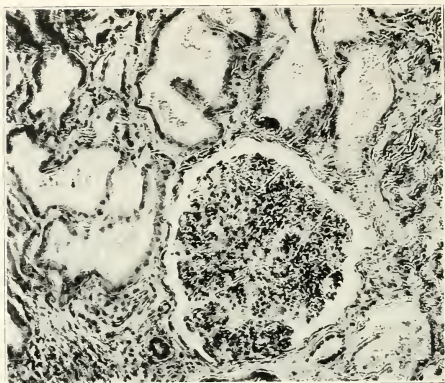


Fig. 9.—Remarkable sized, richly nuclear glomerulus, surrounded by bizarre shaped dilated tubules. ( $\times 165$ .)

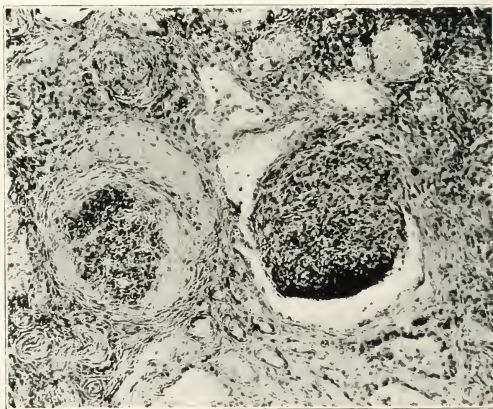


Fig. 10.—Two enormous glomeruli are shown. One is richly cellular, and possesses an almost normal capsule. The tuft of the other is shrunken and has a greatly thickened hyalinized capsule. ( $\times 165$ .)

insufficient (Tilp<sup>5</sup>). Here we find bizarre, branching, greatly enlarged tubules which are often gathered into collections resembling adenomatous new growth; indeed true adenomas are said to form because of excessive regeneration. Many of the tubules contain mitotic figures or syncytial cell masses, and in many fields the resemblance to fetal structures is most marked.

#### DISCUSSION

In the discussion of this case there are several points which should be disposed of briefly before the question of the relation of the renal anomaly and the nephritis can be taken up. The first concerns the relation of scarlatinal nephritis in early life to the development of chronic nephritis in later years. Adult nephritis is frequently attributed to scarlet fever in childhood and probably incorrectly so in the majority of cases. Certain it is that the little evidence available argues against rather than in favor of this commonly accepted belief. Scarlatinal nephritis, as a rule, either kills or is quite promptly cured, and only occasionally results in chronic nephritis, either as a continuation of the primary renal inflammation or as a sequel later on. Still<sup>6</sup> states that of 281 cases of scarlatinal nephritis, 54 per cent. were cured in four weeks, and that only about 24 per cent. showed albumin after six weeks. Rosenfeld and von Rechtenstamm failed to find a single case of severe nephritis among ninety-three persons who had had scarlatinal nephritis in earlier life, and fifty-two of whom had had an albuminuria when discharged from the hospital. Hill<sup>8</sup> states that chronic nephritis after scarlatinal nephritis is not at all a common condition, and among thirty cases of chronic nephritis in children he found only four which seemed to have followed scarlet fever. Hill quotes Ernberg as having found normal urines in all of forty adults who had had acute nephritis, before the age of 15. We may, therefore, conclude that although chronic nephritis does sometimes follow after scarlatinal nephritis, it is evidently somewhat more rare than the general impression would have it. At least two distinct forms of nephritis occur as complications of scarlet fever, (MacCallum,<sup>9</sup> Reichel,<sup>10</sup> Lohlein,<sup>11</sup> Kaufmann<sup>12</sup>). One

5. Tilp, A.: Regenerations Vorgänge in den Nieren, Habil-schr. Strassburg, 1912.

6. Still, G. F.: Common Disorders and Diseases of Children, Ed. 3, 1915. London, Frowde.

7. Rosenfeld, J., and von Rechtenstamm, M. S.: Chronische Albuminurien nach ueberstandener Scharlach-nephritis, Ztschr. f. Kinderh. **4**:265, 1912.

8. Hill, L. W.: Nephritis of Children, Am. J. Dis. Child. **17**:270 (April) 1919.

9. MacCallum, W.: Textbook of Pathology, Ed. 2, Philadelphia, W. B. Saunders Co., 1920.

10. Reichel, H.: Ueber Nephritis bei Scharlach, Ztschr. f. Heilk. **26**:72, 1905.

11. Löhlein, M.: Ueber Schrumpfnieren, Beitr. z. path. Anat. **63**: 1917.

12. Kaufmann, E.: Spezielle Pathologische Anatomie, Ed. 6, G. Reimer, 1911.



in which the renal function may be but little disturbed, and in which the lesion consists principally of an interstitial infiltration by round cells, mainly plasma cells and lymphocytes. The glomeruli are often little or not at all involved; the tubules may show but little degeneration. This is the acute interstitial (nonsuppurative) nephritis described by Councilman<sup>13</sup> and others. Similar renal lesions occur in certain other acute infections.

In the second form, the glomeruli are particularly involved; they appear considerably swollen, are more nuclear because of proliferation of the capillary endothelium and also the presence within the capillary loops of various leukocytes. Hyaline and other thrombi often occlude the capillary lumen and render some or all the loops bloodless. An exudate of fibrin, cells and debris is frequently present within the capsular space. The capsular lining cells often proliferate greatly, forming a crescentic outgrowth to which the diseased tuft becomes adherent. This typical glomerulonephritis is apt to occur in the third week of the disease, or may be postscarlatinal. As in all types of glomerulonephritis, secondary degeneration of the tubules, corresponding to the diseased glomeruli, is present. Combination forms of the above types are not infrequently encountered. Concerning the end stages of glomerulonephritis ("chronic" glomerulonephritis), it is generally conceded that an atrophic, more or less evenly granular, fibrous organ may result which is termed "secondary contracted kidney." Little is known about the reparative and terminal stages of the acute interstitial nephritis (nephritis interstitialis cicatricans of Aschoff.) This is principally due to the fact that most patients either die in the acute stage, or only give rise to clinical symptoms and terminate fatally at so late an age period that more or less renal scarring independent of the previous process, exists. In other words, it is possible only very rarely to find an instance in which the terminal stage of scarlatinal nephritis may be studied.

It may be that the present case offers such an opportunity, if we may assume that the scarlet fever was the primary injurious agent and that because of the absence of its fellow, the affected kidney was subjected to so great a strain that a fatal termination took place at an age when fibrous changes in the kidney do not usually occur. Aschoff believes it probable that certain cases of "genuine" contracted kidney (primary contracted kidney, true granular atrophy; true interstitial nephritis) may be traced to the acute interstitial nephritis. This opinion is not fully accepted by Löhlein, but everything in the present case points strongly to the correctness of Aschoff's supposition. It is

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13. Councilman, W. T.: Acute Interstitial Nephritis, *J. Exper. M.* **3**:393 (July) 1898.

possible, therefore, that in this instance a true chronic interstitial nephritis, resulted from what probably was an acute interstitial nephritis.

The second question concerns the occurrence of chronic nephritis before the age of 20. And here we must be careful to differentiate between the usual type of chronic nephritis in childhood and true chronic interstitial or glomerulonephritis. The latter is relatively rare. Heubner<sup>14</sup> states that chronic hemorrhagic nephritis is the characteristic type of chronic nephritis in childhood, and that of seventy-three cases of nephritis in childhood only one was true chronic interstitial nephritis with true contracted kidney. Sawyer<sup>15</sup> also emphasizes its rarity and states that it is only rarely caused by scarlet fever. He does, however, quote four cases in which scarlet fever occurred at 8, 6, 12 and 10 years of age, respectively, and was followed by chronic interstitial nephritis at the ages of 10, 11, 18 and 18, respectively. Much the same picture has been described under the term "contracted kidney secondary to scarlatinal nephritis." True chronic interstitial nephritis may occur at a very early age; several cases under 5 years of age have been reported and Sawyer quotes one at 3½ years. This is interesting in view of the relative immunity of infants to scarlet fever. When it does occur it presents much the same picture as in adults but the increase of blood pressure and hypertrophy of the heart are more variable. Uremia usually terminates the case. Not infrequently true chronic interstitial nephritis in children is associated with mental and physical underdevelopment. Miller and Parsons,<sup>16</sup> in referring to this picture of "renal infantilism," state that it is an accompaniment of chronic interstitial nephritis and that it is not syphilitic, and offers a poor prognosis. Typical cases are very striking. Barber<sup>17</sup> has reported two cases in one family; the children were aged 12 and 14 years respectively, but were markedly underdeveloped. One child died in uremia, and at necropsy the kidneys were very small and showed a typical chronic interstitial nephritis.

It was stated that the blood pressure may not show elevation. This was true in Barber's cases, while Berkley and Lee<sup>18</sup> report a case of chronic interstitial nephritis in a boy of 10 years who had a systolic blood pressure of 250 and a diastolic blood pressure of 190.

14. Heubner, O.: Ueber chronische Nephrose im Kindesalter, *Jahrb. f. Kinderh.* **77**:1, 1913.

15. Sawyer, J. E. H.: Chronic Interstitial Nephritis in Children, *Birmingham M. Rev.* **54**:511 (Aug.) 1903.

16. Miller, R., and Parsons, L.: Renal Infantilism, *Brit. J. Child. Dis.* **9**:289 (July) 1912.

17. Barber, H.: Chronic Interstitial Nephritis in Children, *Brit. M. J.* **2**:1204 (Nov. 8) 1913.

18. Berkley, H. K., and Lee, J. M.: Hypertension, *Am. J. Dis. Child.* **13**: 354 (April) 1917.



The next question concerns the renal anomaly. Complete absence of one kidney (aplasia, agenesis, single kidney) must be distinguished from the horseshoe or solitary kidney, the result of fusion of two kidneys, and from the very small kidney of hypogenesis or of atrophy. The hypogenetic kidney may be extremely small and its presence easily overlooked at necropsy, and in the older records many such cases in all probability are recorded as instances of true agenesis.

Congenital absence of the kidney is believed to be the result of a failure of the Wolffian duct to throw off the corresponding renal bud after the duct has reached the cloaca. Males are twice as frequently affected as females, and it is the left kidney which is more often absent. Congenital anomalies of the genitalia are not uncommonly associated with this renal anomaly, and the genital anomaly is usually on the side of the absent kidney. Guizzetti<sup>19</sup> found that one half of forty-six cases of single kidney showed some genital anomaly, and others have reported a similar figure. It has even been suggested that this finding of a genital anomaly should warn of the possible absence of a kidney.

True agenesis of the kidney is not extremely rare. Dorland<sup>20</sup> quotes the combined statistics of Morris, Petersen, Rootes, Sangalli and Menzies as showing eleven cases in 25,142 necropsies, or one in 2,286. He also refers to the reports by Moore of one in 2,400; Gerard, one in 2,500; and Weir, one in 5,000. Guizzetti found seven in 2,848 necropsies, and also reported an earlier series of thirty-nine in 20,000 necropsies.

The total number of cases of this anomaly reported is quite high. Dorland, in 1909, placed the total at 300, while Anders, in 1910, accepted only 286 cases of which he had collected sixty-one cases.

The last question concerns the influence which this, or similar, renal anomalies may have on the existing kidney. It would seem that possibly the existing kidney might suffer simply as a result of the greater demands made on it in the absence of its fellow, or that it might be impaired congenitally as a part of the developmental fault which led to the absence of the opposite kidney. Anders studied this question and came to the conclusion that while longevity is not markedly abridged, yet a greater than the normal percentage among subjects of congenital single kidney die of kidney complaints. He found that in 170 cases in which the renal changes were given, seventy-nine, or 46.5 per cent., showed morbid lesions other than mere compensatory hypertrophy, and that thirty-two cases, or 42.3 per cent. of the fatal cases, showed chronic nephritis. Of these, nineteen were con-

19. Guizzetti, P.: *Sulla Coesistenza di anomalie Renali con Anomalie Genitali*, *Riforma med.* **34**:646 (Aug. 17) 1918.

20. Dorland, W. A. N.: *A Consideration of Renal Anomalies*, *Surg., Gyn. & Obst.* **13**:303 (Sept.) 1911.

sidered chronic interstitial nephritis; two were chronic parenchymatous nephritis, and in eleven the type of chronic nephritis was not specified. In the group of sixty-one cases collected by Anders himself, there were twenty-seven cases in which the single kidney was examined; fifteen showed nephritis. Of this group seven were of the chronic interstitial variety, six were recorded as chronic nephritis, one as chronic parenchymatous nephritis, and one was acute.

These figures of incidence are high, but of the seven cases of chronic interstitial nephritis three patients were over 61 years of age at death, one patient was 45, and none was less than 21; the age at death in the fifteen cases showing various forms of nephritis were as follows: Between 21-30, four cases; 31-40, two cases; 41-50, two cases; 51-60, two cases; 61-70, four cases; over 71, one case. It is evident, therefore, that a number of these patients died at an age when the finding of some chronic nephritis is not at all unexpected. Anders' figures, though no doubt correct, may perhaps be somewhat too high from this point of view but there is no reason to doubt his conclusions.

Sometimes the single kidney is dystopic and may even be found in the pelvis. Rolleston<sup>21</sup> reported one such case and collected six others from the literature; only one of these seven was known to have any renal disease but that one died at the age of 10 in uremia from parenchymatous nephritis. Rolleston remarks that the dystopic kidney is especially liable to disease and that this liability is remarkably increased if it is a single kidney. Schaaning makes the same statement concerning the solitary, or fused, kidney and the misplaced kidney, that they are peculiarly liable to disease.

Hypogenesis of the kidney is an anomaly which in a varying degree places the existing renal tissue under similar conditions as does agenesis of one kidney. In fact, when one appreciates that the hypogenetic kidney may weigh less than 1 gm., and be found only by microscopic examination, it is obvious that from the point of view of renal function and strain on the existing kidney there is little or no difference between marked hypogenesis and complete agenesis. Embryologically, there may be an important difference, and the nature of the developmental fault may influence the vitality of the functioning kidney tissue, but this is beyond our present knowledge.

Coplin contends that there is a type of renal anomaly of developmental origin which predisposes to or renders inevitable some form of nephritis. He refers particularly to hypogenesis rather than to agenesis, and he believes that the original fault is probably primarily a defective arteriogenesis. In the group of cases which he describes, the hypogenesis varies considerably. In some cases one kidney is very small while the other is normal or even shows hypertrophy; in other

21. Rolleston, J. D.: Pelvic Kidney, *Brit. J. Child. Dis.* **13**:80 (March) 1916.

cases both kidneys are much below the normal size, just as in the agenetic group the association of genital anomalies and dystopia of the kidney is not infrequent. Concerning the liability of such patients to nephritis, Coplin says: "of nine cases embraced in this study, in three, renal disease was clearly indicated, and in one the diagnosis of chronic interstitial nephritis was made with full recognition of associated cardiovascular phenomena; in another the diagnosis was chronic nephritis." Coplin concludes that "nephritis, toxemia, or uremia coming on in young persons without adequate cause should arouse suspicion." He evidently feels that this anomaly renders the subject liable to nephritis, but he acknowledges that patients may reach old age without any symptoms. A call at any time for unusual functional activity of the kidney may cause a breakdown.

Babes reported six cases which closely resemble Coplin's cases, and which clinically are very like our case. His patients were all under 30 years of age; they were anemic and below par. Each patient developed after some minor infection a sudden onset of uremic symptoms leading rapidly to death. The urine was quite abundant, of low color, and contained considerable amounts of albumin and casts. There was some left ventricular hypertrophy and the pulse was hard. Epistaxis, hemoptysis and purpura were not uncommon. At the necropsy the kidneys were both present but one or both were very small, lower in position than normal and supplied by a renal artery smaller than normal. One kidney sometimes weighed as little as 20 gm., and in two instances one kidney was almost agenetic while the other was hypertrophied. Microscopically, the picture was neither a simple nephritic sclerosis nor a simple arteriosclerosis, nor does Babes consider the condition a simple arterial inadequacy, but a true hypogenesis, perhaps, with a superadded nephritis. Jianu and Meller<sup>22</sup> followed up Babes' work with further observations but added nothing new.

This brief summary of the evidence certainly justifies the opinion that the renal anomalies, agenesis, hypogenesis and possibly dystopia are associated with a greater than normal liability to chronic nephritis. Some of the evidence suggests that nephritis is not the only form of renal disease to which such individuals are subject, but that stone, tuberculosis, etc., are also frequently associated. This is, however, outside the question under discussion.

Why the single kidney should be liable to nephritis is not known. Speculation may follow the two lines previously suggested. Undoubtedly the absence, or extreme hypogenesis, of one kidney results in an increased demand on the other kidney which might well be thought to

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22. Jianu, J., and Meller, O.: Einige Bemerkungen über hypogenetische Nephritis, *Centralbl. f. allg. Path. u. path. Anat.* **23**:774 (Sept. 15) 1912.

be sufficient to result, in many instances, in nephritis. This explanation is not so adequate for the cases in which the opposite kidney shows hypertrophy, nor do the results after nephrectomy add strength to the hypothesis. Nor do the cases of bilateral moderate hypogenesis seem to bear it out. Finally, it is impossible to explain on a simple quantitative reduction in renal tissue the tendency to nephritis described in fused kidneys or in dystopic kidneys.

On the other hand, there is the hypothesis that the congenital maldevelopment has also influenced the single kidney in the case of agenesis, or the apparently normal kidney opposite the markedly hypogenetic one. This hypothesis seems the more reasonable but would seem to be open to pathological demonstration. A congenital influence sufficient to render the kidney liable to chronic disease might, perhaps, be expected to show some sign although it is possible that this very occurrence is common but unrecognized.

In the group of hypogenetic kidney cases Coplin argues for a primary defective arteriogenesis while Babes claims that there is present a true congenital alteration of structure. These statements only indirectly enter into the question of the single kidney concerning which there is less evidence. Many of the single kidneys are noted as having marked fetal lobulations as did our own case. Dorland, however, states that the single kidney is almost always normal in shape, but Rolleston mentions fetal lobulations. There is no known evidence, however, to suggest that fetal lobulations per se are indicative of lowered functional efficiency. It seems at least possible that the various groups of cases briefly touched on above and which all have certain points in common must surely be correlated in some manner and must have some factor common to all to explain the evident tendency to nephritis. Certain it is that in all these cases the renal function is easily impaired and that the renal factor of safety is reduced.

When one considers the case herein reported from the point of view of the anomaly and the subsequent nephritis, one is struck by the similarity which it bears to the groups discussed by Coplin, Anders and Babes. This is true, not only of the clinical picture, but also, of certain aspects of the kidney itself. But even granting the absence of one kidney and some congenital malformation of the other, this does not complete the story. In every instance there must be some additional factor, some actual cause of the nephritis. That this factor is often overlooked is to be explained on the apparently unimportant nature of the injury which would be sufficient to bring about nephritis in such handicapped individuals. Perhaps, the same trifling causes which in normal individuals bring about the chronic nephritis of adult years would be capable in individuals with renal anomalies of bringing about a similar renal disease at a much earlier age.

In our case the problem is, perhaps, simplified by the attack of scarlet fever; for although there is no positive evidence, the history of ill health dating from the scarlatinal attack and the renal changes found at necropsy suggest that a scarlatinal nephritis occurred. As has been said, such a scarlatinal nephritis in an otherwise normal individual either promptly leads to a fatal outcome, or is apparently cured; no evidence of chronic nephritis appearing until, at least, many years after. In our patient, however, the existence of the renal anomaly brought about in an unusually short time a fatal degree of chronic nephritis.

#### SUMMARY

1. A clinicopathologic study is reported of a fatal case of renal disease in a 14 year old girl.

2. The clinical picture was that of a uremia terminating a chronic interstitial or glomerular nephritis. All the usual evidences, both clinical and laboratory, were present. In addition there was a marked purpuric tendency.

3. The postmortem disclosed aplasia of the left kidney; histopathologic study of the small right kidney showed a combination of true chronic interstitial nephritis and chronic glomerulonephritis. A remarkable degree of regeneration was seen, which, however, was morphologically and functionally insufficient (frustrated regeneration).

4. An attempt to weigh the evidence concerning etiology leads to the tentative conclusion that this unusual picture was the result of the injurious action of scarlatina initiating a nephritis, which, because of the inadequate and possibly anomalous kidney present, rapidly resulted in a condition analogous to chronic nephritis of adults.

# I. LIVER REGENERATION FOLLOWING CHLOROFORM INJURY AS INFLUENCED BY THE FEEDING OF CASEIN OR GELATIN \*

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SAN FRANCISCO

This paper continues the investigation of liver cell repair as influenced by diet factors. Other papers<sup>1</sup> show the influence of meat, fat and carbohydrate feeding on the reconstruction of liver cells. It has been pointed out that a uniform central liver necrosis involving half or more of the liver cells can be readily produced by chloroform anesthesia or chloroform injection following a standard fasting period. Under favorable diet conditions this liver necrosis may be completely repaired by the formation of new liver cells in a period of from seven to ten days. The solution or autolysis and removal of the dead liver cells precedes the construction of new liver cells. The construction of this great mass of liver cells is a truly remarkable reaction which is worthy of much study. This speed of growth or reproduction far exceeds the new growth seen in the most malignant neoplasms or even growing embryonic tissues. It seemed highly desirable to study this new formation of specialized cells to determine the factors which may control, favor or hamper the cell reconstruction.

It is very significant that abundant carbohydrate feeding (cane sugar) is quite favorable to rapid liver cell repair and complete cell repair may be attained without the intake of any nitrogenous material. This shows very careful conservation of nitrogenous fractions in the body and proves that sugar may at times act directly by conservation of protein split products in its protein sparing action.

Glycogen is so intimately concerned in the life cycle of the liver cell that possibly sugar feeding has greater influence for the rapid development of liver cells than of other body cells. Fat apparently is not concerned in this liver cell repair and in the diet under such conditions seems to be inert, although furnishing energy requirements.

The repair and construction of red blood cells have been studied in this laboratory<sup>2</sup> and stand in marked contrast to the liver cell construction. Carbohydrate has a minimal influence on the red cell con-

\* From the George Williams Hooper Foundation for Medical Research, University of California Medical School.

† University of California Fellowship.

1. Davis, N. C.; Hall, C. C., and Whipple, G. H.: *Arch. Int. Med.* **23**:689 (June) 1919. Davis, N. C., and Whipple, G. H.: *ibid.* **23**:711 (June) 1919.

2. Whipple, G. H.; Hooper, C. W., and Robschey, F. S.: *Am. J. Physiol.* **53**:167, 1920.

struction as contrasted with meat proteins, for example. This indicates wide individual variation in the repair or reconstruction complex of various body cells.

We hope to study the influence of several simple proteins and protein split products upon this standard repair of liver cells. At this time we wish to report in detail the experiments dealing with two common proteins, one of which (casein) is a complete protein and the other (gelatin) an incomplete protein.

Casein may be considered a representative of the "complete proteins" (Abderhalden, Fischer, and others). The amino-acid glycocholic acid, which is absent, is known to be synthesized in animal metabolism when needed. The content of cystine is relatively low. Gelatin<sup>3</sup> is quite high in glycocholic acid, but lacks the important amino-acids tyrosine, tryptophan and cystine, and is, therefore, an "incomplete protein." Both casein and gelatin are readily obtained commercially in a comparatively pure condition.

It is interesting to compare the assistance given by such different substances in the rapid repair of body tissue. Obviously our short feeding experiments of seven to ten days are not comparable with the long continued growth and general maintenance experiments.

#### METHOD

The routine of our regeneration experiments has been described elsewhere.<sup>1</sup> In brief: The animal is starved for a short period; a liver injury is obtained either by chloroform anesthesia or by subcutaneous injection of chloroform; feeding is begun the day after administration of the drug; a biopsy specimen for microscopic examination is removed from the liver on the second day (this shows the initial injury, with practically no repair); feeding is continued for any desired period following operation, usually about seven days; a liver specimen is then secured either by another operation or by sacrifice of the animal (this shows the amount of regeneration which has taken place in the liver parenchyma). An animal may frequently be used for two or more experiments.

Dogs seldom eat pure gelatin or pure casein from their food pans in any considerable amounts. It has been found satisfactory, though somewhat laborious, to make a thin casein mush in warm water and feed it to the animals by spoon. Gelatin is always given in warm solution by stomach tube. A suitable amount of salt is given with both substances. The animals will often retain their food better if the desired ration is given in divided doses throughout the day.

3. Fischer, E.; Levene, P. A., and Aders, R. H.: *Ztschr. f. physiol. Chem.* **35**:70, 1902. Levene, P. A., and Beatty, W. A.: *Ibid.* **49**:252, 1906.

## EXPERIMENTAL OBSERVATIONS

In the accompanying table are summarized the results of feeding experiments with casein and gelatin. Protocols follow.

## LIVER REPAIR INFLUENCED BY FEEDING OF CASEIN AND GELATIN

Experiment	Liver Injury	Feeding, Days	Average Daily Amount Food, Gm.	Liver Repair	Remarks
<b>Casein</b>					
No. 1 Dog 20-41	55-60% necrosis; trace of fat	8	100	20% unrepaid; no fat	Some vomiting on 2d day; developed distemper; killed
No. 2 Dog 20-66	60-65% necrosis; slight trace of fat	9	120	15% unrepaid	Vomiting on 2d day; bright and active
No. 4 Dog 20-111	50-55% necrosis; fat moderate	~	100	20-25% unregenerated; fat heavy around central veins	Vomiting on 3d day; wound broke down; killed
No. 5 Dog 21-18	30-35% necrosis; trace of fat	9	100	Regeneration prac- tically complete	No vomiting; maintained weight
No. 8 Dog 21-26	45-50% necrosis; fat heavy to lobule periph- eries	9	60	10-15% unregener- ated; fat moder- ate	No vomiting; died under anesthesia at final operation; necropsy negative
<b>Gelatin</b>					
No. 3 Dog 20-66	60-65% necrosis; sligh. trace of fat	9	68	15% unrepaid; slightest possible trace of fat	Vomiting on 4th day; bright and active
No. 6 Dog 21-18	60-65% necrosis; fat heavy to lobule periph- eries	9	100	Regeneration prac- tically complete; heavy trace of fat in central cells	Vomiting on 3d day; weak toward end of experiment
No. 7 Dog 21-26	60-65% necrosis; fat heavy to lobule periph- eries	9	60	10% unregenerated; fat moderate	Vomiting on 8th day; bright and active
No. 9 Dog 20-77	20-30% necrosis; severe injury up to 40%; slight scat- tering of fat	9	50	Regeneration prac- tically complete; slightest possible trace of fat	Vomiting on 2d day; in good con- dition throughout
No. 10 Dog 20-106	60% necrosis	9	65	10-15% unre- generated	No vomiting; died under anesthesia at 2d operation; kidney sections show slight ne- phritis

## EXPERIMENT 2.—Casein Feeding. Dog 20-66. White mongrel male.

Jan. 8, 1920. Weight, 21.12 pounds. Just recovered from distemper; in good condition. Isolated for starvation after daily feeding.

January 9, 10 and 11. No food.

January 12. Weight, 19.5 pounds. Active. Chloroform anesthesia, 1 hour (5:10 to 6:10 p. m.).

January 13. Weight, 19.5 pounds. Active. Left 125 gm. casein, and salt, and a little beef extract (all moistened) in cage.

January 14. Weight, 19 pounds. Active. Ate about 75 gm. casein left in cage. Piece of liver removed at 2:30 p. m. Vomited later. Left a little casein in cage—no forced feeding.

January 15. Weight, 18.5 pounds. Bright and active. 120 gm. casein by spoon feeding.



January 16. Weight, 19 pounds. Bright and active. 125 gm. casein by spoon feeding.

January 17. Weight, 18.7 pounds. Bright and active. 125 gm. casein by spoon feeding.

January 18. Weight, 18.7 pounds. Bright and active. 125 gm. casein by spoon feeding.

January 19. Weight, 18.4 pounds. Bright and active. 125 gm. casein by spoon feeding.

January 21. Piece of liver removed at 2:30 p. m.

January 28. Wounds almost well. In excellent condition.

Sections: First operation, from 60 to 65 per cent. necrosis. Slight trace of fat.

Sections: Second operation, 15 per cent. unrepaid.

EXPERIMENT 5.—*Casein Feeding*. Dog 21-18. Young brindle mongrel, male.

Sept. 14, 1920. Weight, 25.5 pounds. In good condition. Old keratitis and staphyloma of right eye suggest previous distemper infection. Isolated after daily feeding: fasting begun.

September 15, 16 and 17. No food.

September 19. Weight, 23.8 pounds. Chloroform anesthesia for forty-five minutes (3 to 3:45 p. m.). Gave 10 mg. sodium cyanid in 100 c.c. physiologic sodium chlorid solution intravenously during thirty-five minutes of anesthesia.

September 18. Weight, 23.3 pounds. A little dull. Gave 100 gm. casein and salt by spoon feeding.

September 20. Weight, 23.5 pounds. A little dull. Gave 100 gm. casein and salt as before. Piece of liver removed at 3 p. m. Liver looks injured in gross.

September 21. Weight, 23.25 pounds. Dull. Nose shows slight discharge. 100 gm. casein.

September 22. Weight, 23.4 pounds. Dull. Nose shows slight discharge. 100 gm. casein.

September 23. Weight, 23.4 pounds. Wound infected, but not broken down. 100 gm. casein.

September 24. Weight, 23.7 pounds. Nose condition clearing up. 100 gm. casein.

September 25. Weight, 23.7 pounds. No nasal discharge. Thin purulent oozing from wound. 100 gm. casein.

September 26. Weight, 23.8 pounds. Constipation probably accounts for some of gain in weight. 100 gm. casein.

September 27. Weight, 23.7 pounds. Wound superficially open. 100 gm. casein. Operation at 2:30 p. m. Small piece of liver removed.

Sections: First operation, from 30 to 35 per cent. necrosis; trace of fat.

Sections: Second operation, almost complete regeneration; less than 10 per cent. not filled out. Slightest possible trace of fat.

EXPERIMENT 6.—*Gelatin Feeding*. Dog 21-18. Young brindle mongrel, male.

Oct. 19, 1920. Weight, 30.7 pounds. Former operative sites in good condition. Isolated after daily feeding; fasting begun.

October 20, 21 and 22. No food.

October 23. Weight, 27.5 pounds. Active and in good condition. Chloroform anesthesia for forty-five minutes (3:40 to 4:25 p. m.). 100 c.c. physiologic sodium chlorid solution intravenously during anesthesia.

October 24. Weight, 27 pounds. Active. 100 gm. gelatin and salt in 300 c.c. water by stomach tube.

October 25. Weight, 25.5 pounds. Active. No vomiting. 100 gm. gelatin given in divided doses. Piece of liver removed at 2:30 p. m.

October 26. Weight, 25.5 pounds. Bright and active. 100 gm. gelatin in divided doses (partly vomited).

October 27. Weight, 25.4 pounds. Active. 100 gm. gelatin as before. No vomiting.

October 28. Weight, 25 pounds. Rather quiet. 100 gm. gelatin as before. No vomiting.

October 29. Weight, 25.1 pounds. Quiet and somewhat weak. 100 gm. gelatin as before. No vomiting.

October 30. Weight, 25.25 pounds. Rather weak. Removed stitches yesterday evening and wound has opened because of infection. 100 gm. gelatin in divided doses. No vomiting.

October 31. Weight, 24.75 pounds. Seems bright, but not active. 100 gm. gelatin at one feeding. No vomiting.

November 1. Weight, 24.5 pounds. Inactive. 100 gm. gelatin at one feeding. No vomiting. Piece of liver removed at 3:30 p. m.

Sections: Third operation, from 60 to 65 per cent. necrosis; fat heavy to lobule peripheries.

Sections: Fourth operation, almost complete filling in of lobules (less than 10 per cent. unregenerated); lobule centers show heavy trace of fat.

EXPERIMENT 7.—*Gelatin Feeding.* Dog 21-26. Young, long-haired mongrel, female.

Oct. 5, 1920. Weight, 18.8 pounds. In good condition: active. Isolated after daily feeding; fasting begun.

October 6, 7 and 8. No food.

October 9. Weight, 16.9 pounds (7.7 kilos). Active. Chloroform anesthesia for forty-five minutes (3:35 to 4:20 p. m.). During forty minutes of this time 260 c.c. of 1 per cent. sodium carbonate in hypertonic saline solution (1.4 per cent.) were given intravenously (approximately 34 c.c. per kilo).

October 10. Weight, 16.25 pounds. Bright and active. Gave 60 gm. gelatin and salt in 200 c.c. water by stomach tube.

October 11. Weight, 16.5 pounds. Active. No vomiting yesterday. 60 gm. gelatin. Piece of liver removed at 4 p. m. Liver looks fatty.

October 12. Weight, 16.4 pounds. Quiet. 60 gm. gelatin by stomach tube (lost a little).

October 13. Weight, 15.75 pounds. More active today. 60 gm. gelatin. No vomiting.

October 14. Weight, 15.5 pounds. Rather quiet. 60 gm. gelatin in divided doses. No vomiting.

October 15. Weight, 15.4 pounds. Quite active. 30 gm. gelatin in morning, 60 gm. in evening.

October 17. Weight, 14.5 pounds. Active. 75 gm. gelatin. Wound open a little.

October 18. Weight, 14.6 pounds. Bright and active. 75 gm. gelatin (Vomited some last night.) Piece of liver removed at 2:30 p.m. Encountered a little peritoneal fluid, slightly cloudy.

Sections: First operation: 45 to 50 per cent. necrosis; fat heavy to lobule peripheries.

Sections: Second operation: about 10 per cent. unregenerated; fat moderate.

EXPERIMENT 8.—*Casein Feeding.* Dog 21-26. Young, long-haired mongrel, female.

November 16, 1920. Weight, 18.9 pounds. In good condition. Dog had a touch of distemper since last used, but has recovered. Isolated after daily feeding; fasting begun.

November 17, 18 and 19. No food.

November 20. Weight, 16.6 pounds (7.55 kilos). In good condition, active. Chloroform anesthesia for forty-five minutes (2:05 to 2:50 p. m.). During forty minutes of this period 260 c.c. hypertonic saline solution (1.4 per cent.) was given intravenously (34 + c.c. per kilo).

November 21. Weight, 16 pounds. Bright and active. 60 gm. casein and salt by spoon feeding.

November 22. Weight, 16.5 pounds. Bright and active. 60 gm. casein and salt by spoon feeding. Some casein was vomited yesterday. Piece of liver removed at 12 noon; fatty and friable.

November 23. Weight, 16.25 pounds. Somewhat weak. There appears to have been some oozing from wound. 60 gm. casein in divided doses.

November 24. Weight, 16 pounds. Bright and active. 60 gm. casein in divided doses.

November 25. Weight, 16 pounds. Bright and active. 60 gm. casein at one feeding.

November 26. Weight, 16.1 pounds. Bright and active. 60 gm. casein at one feeding.

November 27. Weight, 15.9 pounds. Bright and active. 60 gm. casein at one feeding.

November 28. Weight, 15.6 pounds. Bright and active. 60 gm. casein at one feeding. Wound healing nicely.

November 29. Weight, 15.4 pounds. Bright and active. 60 gm. casein at one feeding. Operation in afternoon; dog died under anesthesia. Necropsy essentially negative.

Sections: Third operation: from 45 to 50 per cent. necrosis; fat heavy to lobule peripheries.

Sections: Necropsy: from 10 to 15 per cent. unregenerated; fat moderate.

EXPERIMENT 9.—*Gelatin Feeding.* Dog 20-77. Young female terrier.

Feb. 21, 1920. Weight, 11.5 pounds. Active and in good condition. Isolated after daily feeding; fasting begun.

February 22, 23, 24 and 25. No food.

February 25. Weight, 10 pounds. Active. Chloroform anesthesia one hour and ten minutes (3:20 to 4:30 p. m.).

February 26. Weight, 9.5 pounds. Active. 50 gm. gelatin in 200 c.c. water by stomach tube.

February 27. Weight, 9.5 pounds. Active. 50 gm. gelatin in 200 c.c. water by stomach tube. Food partly vomited. Piece of liver removed at 10:30 a. m.

February 28. Weight, 9.5 pounds. Active. 50 gm. gelatin by stomach tube.

February 29. Weight, 9.1 pounds. Active. 50 gm. gelatin by stomach tube.

March 2. Weight, 8.75 pounds. Active. 50 gm. gelatin by stomach tube.

March 2. Weight, 8.6 pounds. Active. 50 gm. gelatin by stomach tube.

March 3. Weight, 8.4 pounds. Active. 50 gm. gelatin by stomach tube.

Operation wound opening slightly.

March 4. Weight, 8.2 pounds. Rather quiet. 50 gm. gelatin by stomach tube.

March 5. Weight, 8.2 pounds. Rather quiet. 50 gm. gelatin by stomach tube. 3:30 p. m., removed piece of liver.

Sections: Second operation: from 25 to 30 per cent. necrosis, injured up to 40 per cent. with scattering of fat.

Sections: Third operation; slightest possible trace of fat; repair almost complete.

The following experiments were undertaken with the idea of supplementing a sugar diet with casein. The protein was digested with pancreatic extract so that it became soluble. Since the digest was very nauseating, an attempt was made in one experiment to give it by the intraperitoneal route. In addition to the animals in Experiments 12 and 13, another dog was given sugar and casein digest by stomach tube. This dog died on the sixth day after chloroforming with very toxic symptoms and autopsy showed less than one-half of the liver injury repaired.

It is clear that this casein digest amino-acid mixture was much more toxic to a dog poisoned by chloroform than to a normal animal. The significance of this observation is not apparent but further investigation of this point should be made.

EXPERIMENT 11.—*Casein Digest Intraperitoneally. Control. Dog 20-78.*  
Long-haired mongrel, male.

Feb. 4, 1920. Given 5 gm. casein digest dissolved in 35 c.c. physiologic sodium chlorid solution, intraperitoneally. No reaction.

February 5 and 6. Dog clinically as usual.

February 7. 10 gm. casein digest intraperitoneally. No reaction.

Feb. 8 and 9. As well as usual.

February 10. Sacrificed. Necropsy negative.

EXPERIMENT 12.—*Sugar Feeding; Casein Digest Intraperitoneally. Dog 20-64.*  
Large, black spaniel, female.

Feb. 7, 1920. Weight, 33.75 pounds. In excellent condition. Isolated after daily feeding; fasting begun.

February 8, 9 and 10. No food.

February 11. Weight, 29.6 pounds. Active. Chloroform anesthesia for one hour and five minutes (3:30 to 4:35 p. m.).

February 12. Weight, 29.2 pounds. Bright and active. 100 gm. cane sugar and kaolin by stomach tube.

February 13. Weight, 28.6 pounds. Somewhat dull and weak. Food as yesterday. Piece of liver removed at 3:45 p. m.; gross appearance of severe injury. (Sections show from 50 to 55 per cent. necrosis.)

February 14. Weight, 29 pounds. Dog is quite sick. Pulse rapid and weak; temperature subnormal. No jaundice or hemorrhages; 100 gm. cane sugar by stomach tube; 5 gm. protein digest intraperitoneally in 25 c.c. water. All intraperitoneal injections given under light ether anesthesia.

February 15. Weight, 29.3 pounds. Weak, but not so sick as yesterday. Sclera jaundiced. 100 gm. sugar by stomach tube; 5 gm. protein digest in 20 c.c. fluid intraperitoneally.

February 16. Weight, 28.3 pounds. Still weak. 100 gm. sugar by stomach tube; 10 gm. protein digest in 45 c.c. fluid intraperitoneally.

Feb. 17. Weight, 28 pounds. Sugar as before; 10 gm. protein digest in 30 c.c. fluid intraperitoneally.

February 18. Weight, 27.6 pounds. 150 gm. sugar by stomach tube; 15 gm. protein digest in 45 c.c. water intraperitoneally.

February 19. Weight, 27.25 pounds. Sugar and protein digest as yesterday. Weak.

February 20. Weight, 25.1 pounds. Sugar and protein digest as yesterday. Vomited a little. Very weak. Great quantities of thin, reddish-brown diarrhea. Died about noon.

*Necropsy Report.*—All tissues intensely jaundiced. Some hemorrhage into abdominal wall, especially around operative site and points of injection. Peritoneal cavity contains some fluid, perhaps largely from injection in morning; fluid looks blood tinged. Peritoneal surfaces and mesentery are engorged and purplish; there are occasional fibrin deposits; a loop of intestine is adhered to anterior wall on left side. Fat overlying pericardium appears hemorrhagic. Heart negative. Blood is massively clotted.

Lungs are mottled light and dark (mostly posterior), but there seem to be no hemorrhages or consolidation.

Liver, in addition to jaundice, is extremely mottled, suggesting great lack of repair. There are a number of small antemortem clots throughout the parenchyma.

Spleen shows extensive hemorrhages.

Kidneys: dark; cortices somewhat swollen and cloudy, suggesting parenchymatous degeneration.

Mucosa of gastro-intestinal tract and bladder negative.

*Microscopic Report.*—Lungs: hemorrhagic exudate; congestion. Spleen and lymph nodes: hemorrhages and necrosis. Liver: from 10 to 15 per cent. not repaired. Kidneys: cloudy swelling.

EXPERIMENT 13.—*Sugar and Casein Digest Feeding. Dog 20-76. Black mongrel, female.*

April 28, 1920. Weight, 14.75 pounds. In good condition (three previous experiments). Isolated after daily feeding; fasting begun.

April 29 and 30. No food.

May 1. Weight, 13.25 pounds (6.023 kilos). Dog in good condition. Gave 1.27 c.c. chloroform (0.21 c.c. per kilo) plus twice its volume liquid petrolatum subcutaneously.

May 2. Weight, 13.1 pounds. Bright and active. Gave by stomach tube 50 gm. cane sugar, 15 gm. protein digest and a little kaolin.

May 3.—Weight, 12.9 pounds. Vomited some yesterday. Food as yesterday except 5 gm. less amino-acids. Vomited some about one and a half hours after feeding. Operation at 2:30 p. m. Cut out one of preceding operative scars: no difficulties. Piece of liver removed.

May 4. Weight, 12.6 pounds. Active. Fed 100 gm. cane sugar and 15 gm. protein digest in divided doses, by stomach tube.

May 5. Weight, 12.3 pounds. Active. Food as yesterday. Some vomiting in morning.

May 6. Weight, 12.1 pounds. Active. Food as yesterday. Some vomited in morning. Put dog in metabolism cage; to receive less water.

May 7. Weight, 12 pounds. Quiet. Food as yesterday. Not vomited.

May 8. Weight, 11.4 pounds. Quiet. Food as yesterday. Partly vomited.

May 9. Weight, 11 pounds. Quiet. Gave 50 mg. cane sugar and 15 gm. protein digest. Largely vomited.

May 10. Dog is quite weak. Operation at 11 a. m.

The value of the experiment is much decreased because of vomiting. On some days there was little or no vomiting, and when it did occur it was often late; however, probably one third or one half of food was lost. Feces were passed on three occasions during experiment, small amounts of soft, brown material.

Operation on Second Day: 45 to 50 per cent. necrosis; fat moderate.

Operation on Ninth Day: about 15 per cent. unregenerated; trace of fat.

Note: Casein digest yields only 28 mg. amino-nitrogen per gram, indicating that approximately 17.5 per cent. of mixture consists of amino-acids.

#### DISCUSSION

A comparison of the liver regeneration on diets of casein and gelatin shows that in this series the results have been about the same,—the superiority, if any, resting with gelatin. This means that the liver cells were not repaired entirely by amino acids coming from the gelatin, but that the latter must necessarily have been supplemented by "building stones" from endogenous katabolic waste material perhaps in part from the necrotic liver cells.

Regeneration with these isolated proteins has been equal to that with meat diets, better than that on starvation or with fat diet, and less complete than that with mixed table scraps, bread and milk, or even a pure carbohydrate diet.<sup>1</sup> One might infer that in the rapid regeneration of liver cell protein the conservation of metabolic end products plays a larger part than the furnishing of new protein material. Evidently, under certain conditions, energy requirements have precedence over reparative processes to the extent that incoming protein material may be stripped by de-aminization, to a point where synthesis of cell protoplasm is hampered.

Owing to the tendency to vomiting, it has usually been necessary to give less of gelatin than of casein per day. Loss of weight has been less marked in the case of casein feeding.

In experiment 7, carbonate solution was given intravenously during chloroform anesthesia, while in Experiment 8 on the same dog only saline solution was injected, yet the injuries were identical. Whether or not chloroform causes an acidosis, and this in turn is relieved by alkaline therapy, has no bearing on our work—carbonate solution intravenously certainly is not able to prevent in any measure the liver injury caused by chloroform.

#### SUMMARY

Gelatin, although an "incomplete protein," seems to be equally as efficacious as casein in the regeneration of liver parenchyma destroyed by chloroform.

After a 50 to 60 per cent. necrosis, a feeding period of nine days with either substance will restore the liver to within 10 or 15 per cent. of normal. This liver cell regeneration is comparable to that obtained with a meat diet, approaches that given by a high carbohydrate diet, is definitely less than with a full mixed diet, but greater than with a fat diet or with fasting.

The liver repair on gelatin feeding emphasizes again the important fact that the body is able to conserve certain amino acids or split products from its endogenous wastage products and recast these groups into the complex liver cell.

# STUDIES IN THE RESPONSE OF THE CIRCULATION TO LOW OXYGEN TENSION. IV

## A SPHYGMOGRAPHIC STUDY OF THE PULSE DURING THE REBREATHING TEST

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In the examination of candidates to be placed on a flying status, and in the re-examination of aviators, it has occasionally happened that sufficient weight has been given to the occurrence of irregularities in the pulse to disqualify the subject for a flying status, or to give him a lower rating than that to which he would otherwise be entitled. Some apprehension has also been expressed in regard to the development of arrhythmias at lowered oxygen tension.

The work in this paper was to determine what, if any, were the effects of lowered oxygen tension on the rhythm of the heart, as determined by means of the sphygmograph. The tests were done at the Medical Research Laboratory of the Air Service, at Hazelhurst Field, Mineola, Long Island, N. Y. The subjects were for the most part aviators appearing for discharge, after varying periods of service. These were supplemented by a few from the laboratory personnel. In a body of men of as carefully selected physical types as found in the air service, our work was necessarily confined to subjects with very normal cardiovascular mechanisms.

The subjects were all given a preliminary physical examination before the low oxygen test was made. The test was made on the type of rebreathing apparatus in use in the United States Army for the examination and classification of aviators. This apparatus has been fully described elsewhere.<sup>1</sup> In the test by the rebreather method the respiratory system of the subject is part of a closed circuit of known capacity, so that as oxygen is consumed at each respiration, a lowered percentage results in the air chamber from which the subject breathes. The expired air is freed of carbon dioxide by passing through a potassium hydrate cartridge on its return to the air chamber. The oxygen percentage is estimated from the air remaining in the tank at the close of the test, and from this the altitude is estimated. A Mackenzie ink polygraph was attached to the left arm of the subject. Tracings were taken for one minute duration at five minute intervals, or in about

1. Henderson, Yandell and Seibert, E. G.: J. A. M. A. **71**:1382 (Oct. 26) 1918.

one-half of the cases taken almost continuously, periodic interruptions being necessary to adjust the instrument following movements of the subject, and to permit the taking of roentgenograms for cooperative work done by Majors Lewald and Turrell,<sup>2</sup> to show the variation in the size of the heart under decreased oxygen percentage.

The pulse rate and the systolic and diastolic pressures were taken at two minute intervals for the first fifteen minutes, and subsequently every minute. The respiration was recorded by means of a spirometer, and the minute volume of air estimated in deciliters, as described elsewhere.<sup>3</sup>

#### EXPERIMENTAL RESULTS

The reaction of the pulse rate to decreased oxygen tension has been described by Major Schneider<sup>4</sup> and by the writers in the preceding paper of this series.<sup>5</sup> The present work has brought nothing new in that relation, except where the rate was taken continuously by means of a polygraph the increase in rate showed an evenly rising curve, without the periodic variations in rate observed in curves plotted from the rate as estimated by counting the pulse at the wrist for twenty second periods each minute.

In general, there was a slight and very gradual increase in rate until the latter part of the test. As the oxygen want was more acutely felt, a marked acceleration began and increased as the test progressed. A terminal fall in rate occurred in six cases. The mechanism and significance of this fall has been considered by us in another paper, based upon an electrographic study of the pulse during the rebreather test.<sup>5</sup>

The systolic and diastolic pressures followed the same general course as described by Schneider. Figure 1 shows typical curves of pulse rate, blood pressure and deciliters of air per minute.

Because of the large part played by mechanical factors, it is not felt that any great stress can be placed on the contour of the pulse tracing, or that any detailed attempt can be made to correlate it with the pressure curves. Conditions of adjustment and of pen pressure were kept as uniform as possible, but in tests lasting from twenty to thirty minutes, where several readjustments were always necessary, variations were unavoidable. In general it was observed that the amplitude of the pulse wave increased during the test as the cardiac response increased and as pulse pressure changed. This is well shown

2. LeWald, L. T., and Turrell, G. H.: *Am. J. Roentgenol.* **7**:67, 1920.

3. *Manual of the Medical Research Laboratory*, Surgeon-General's Office, Division of Aeronautics, U. S. Army.

4. Schneider, E. C.: *J. A. M. A.* **71**:1382 (Oct. 26) 1918.

5. Greene, C. W., and Gilbert, N. C.: *Arch. Int. Med.* **27**:517 (May) 1921.



in Figure 2, in which sections of the pulse tracing are shown taken at intervals through the test. In a few cases where signs of circulatory inefficiency appeared before or with the signs of psychological inefficiency, the amplitude of the pulse wave decreased at the termination of the test. This is shown in Figure 3, where the preceding curves had been similar to those in Figure 2, I, J, and K.

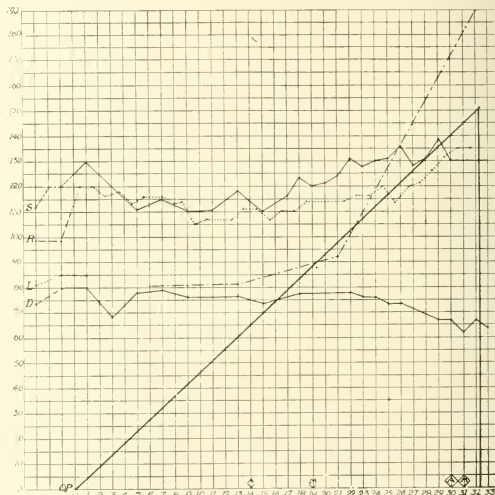


Fig. 1.—A typical response to lowered oxygen tension during rebreather test. S=systolic pressure. D=diastolic pressure. R=pulse rate. L=the respiration in deciliters per minute, the straight unbroken line, OP, the oxygen.

#### DICROTISM

Dicrotism of varying degree was frequently present throughout the entire test but bore no relation to the efficiency of the cardiac response or to the altitude reached. When not present at the beginning of the test it frequently appeared during the latter part of the test and as the systolic pressure rose. It was almost invariably present at the last few minutes of the test, when the systolic pressure was elevated or rising

and the peripheral resistance was decreasing, as evidenced by a falling diastolic pressure and a decrease in the intensity of the second aortic tone.

The increase of dicrotism with increased pulse pressure gives further evidence that a dicrotic pulse is not clinical evidence of a decreased

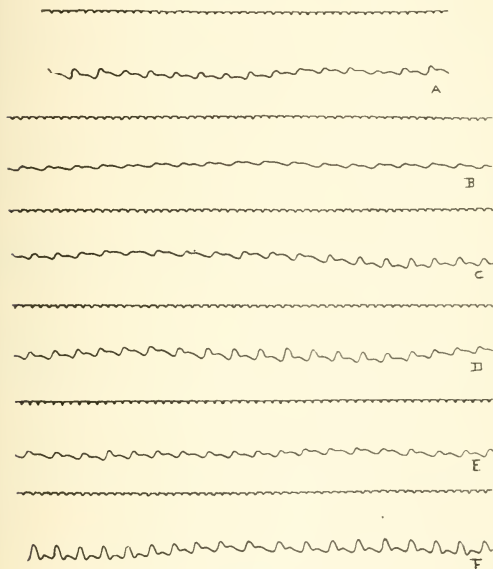


Figure 2A

Fig. 2.—Sections from a typical tracing. A, preliminary tracing; B, 5 minutes; C, 7 minutes; D, 12 minutes; E, 17 minutes; F, 20 minutes; G, 23 minutes; H, 25 minutes; I, 27 minutes; J, 30 minutes; K, taken just as test was terminated because of psychologic inefficiency at 32 minutes and 33 seconds. L, taken directly after conclusion of test; time in one-fifth second.

pulse tension or a lowered cardiac response, a view that one occasionally hears expressed. The degree of dicrotism increases (a) with increased arterial tension, (b) with decreased peripheral resistance. As stated

by Mackenzie." "the presence of a dicrotic wave is evidence of the retention of an important amount of arterial tension." When the cardiac response decreases, the dicrotic wave disappears (Fig. 4).

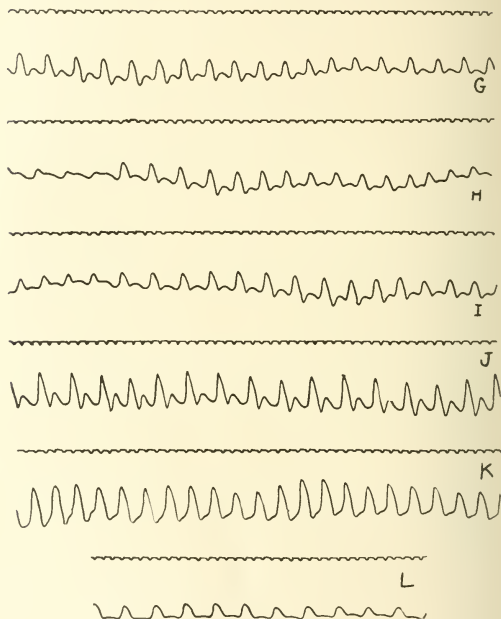


Figure 2 B

Hyperdicrotism appeared under identical conditions when the pulse accelerated during a dicrotic pulse. Hyperdicrotism is under these conditions a direct function of the rate as shown by Mackenzie. This is illustrated in the tracing in Figure 5, where it tends to disappear as

the pulse slows in expiration. The presence or absence of dicrotism did not correlate in any way with the final endurance limit, as expressed in altitude reached.

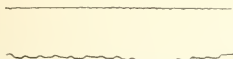
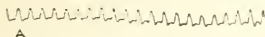
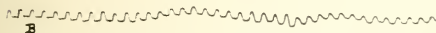


Fig. 3.—Tracing taken just as the test was terminated because of physiological inefficiency at 36 minutes and 26 seconds.



A



B

Fig. 4.—(a) Tracing at 27 minutes, showing dicrotism. Subject responding well. (b) Tracing taken just as subject was taken off of test because of impending unconsciousness. Dicrotic wave has disappeared.

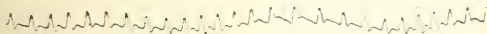


Fig. 5.—Dicrotic waves become hyperdicrotic as pulse accelerates during inspiration, at 17 minutes.

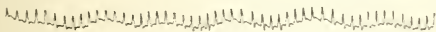


Fig. 6.—Traube-Hering waves.

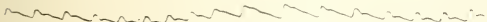


Fig. 7.—Showing sinus arrhythmia at 8 minutes.

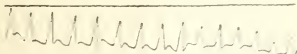


Fig. 8.—Showing a few slightly alternating beats just before the test was terminated at 30 minutes, because of impending unconsciousness.

Traube-Hering waves appeared in several cases during the second half of the test, becoming more pronounced as the test progressed, and disappearing as respiration returned to normal after its conclusion (Fig. 6). In a few instances they were present throughout the test, but

increased in height as the test progressed, and respiratory response increased. They have no bearing upon the altitude reached. Mayer curves, reported in cases of asphyxia, were not observed.

## SINUS ARRHYTHMIA

All of the eighty-one subjects on whom tracings were taken showed some degree of sinus arrhythmia, both before and during the entire test (Fig. 7).

The difference in length between the longest and shortest beats in a given period measured in hundredths of a second, was taken as an

TABLE 1.—PULSE RATE AND THE DEGREE OF SINUS ARRHYTHMIA, IN THE PRELIMINARY TRACING, IN THE FOUR QUARTERS OF THE TEST, AT THE POINT OF TERMINATION OF THE TEST, AND IN THE RECOVERY PERIOD

No.	Age	0%	Rate							Sinus Arrhythmia							Time
			Pr	1	2	3	4	T	R	Pr	1	2	3	4	T	R	
1	26	6.8	72	74	82	86	84	78	63	22	36	38	38	36	40	25	
2	..	....	84	90	76	82	99	60	75	05	25	25	25	15	15	10	
3	24	6.3	63	78	76	78	82	94	63	10	20	40	40	15	10	20	31
4	..	....	62	66	66	75	75	90	57	25	25	40	20	10	05	20	30
5	30	7.4	67	72	82	87	108	112	60	20	15	15	10	05	02	20	28:15
6	25	6.9	57	70	68	68	90	102	56	25	25	50	60	20	10	60	30
7	21	7.2	58	65	68	68	74	78	75	25	30	30	40	30	20	40	39:18
8	23	5.9	74	82	80	84	90	..	78	15	20	20	10	05	..	20	27
9	..	....	72	72	81	81	90	108	84	25	25	25	15	10	05	20	27
10	24	7.2	84	84	88	88	90	96	84	20	25	25	25	20	10	15	
11	..	....	60	75	78	96	120	..	66	25	30	35	15	05	..	20	
12	..	....	66	72	66	75	..	..	60	05	15	20	20	..	..	25	31
13	..	....	66	66	81	84	84	96	72	40	35	40	20	10	..	20	27:30
14	24	6.3	72	84	84	87	96	105	90	10	15	20	10	10	05	20	28
15	22	10.8	66	96	96	..	..	108	84	25	10	10	..	..	05	20	23:50
16	23	10.5	78	84	80	84	102	..	84	20	23	25	20	10	..	20	24
17	27	6.7	81	75	90	96	108	..	78	35	30	20	10	10	..	40	25
18	..	....	72	54	72	78	102	90	66	20	20	30	20	05	05	35	35:27
19	28	8.2	63	67	69	65	65	81	60	45	45	50	60	45	30	30	30:00
20	27	6.5	66	66	69	81	84	102	72	20	20	20	35	20	05	40	28
21	22	8.5	69	70	72	72	78	84	72	10	10	10	10	10	05	10	30:45
22	23	11.9	75	75	75	78	84	75	69	20	25	20	20	20	10	..	
23	25	6.3	72	68	78	78	81	102	84	05	25	25	10	05	60	20	31
24	23	6.2	70	71	78	82	88	96	56	40	40	40	40	25	05	40	30
25	25	7.8	78	78	87	90	99	105	90	20	20	15	10	60	00	25	
26	20	8.4	74	90	81	87	93	96	90	35	30	35	25	25	15	20	26
27	28	11.4	87	78	84	90	90	66	56	25	25	10	10	10	..	30	22
28	26	7.9	66	69	78	68	93	110	90	25	30	40	40	10	60	25	32:55
29	22	7.7	68	80	76	80	108	114	74	25	20	20	15	05	05	30	3:11
30	24	7.5	86	102	96	87	90	120	84	20	25	30	30	10	05	20	30:14
31	27	7.2	62	66	66	66	78	84	60	20	20	20	20	10	10	20	34:17

index of the degree of the sinus arrhythmia during that period. This was measured in the preliminary tracing taken before the test, and at five minute intervals during the test, and charted with the pulse rate at the corresponding period.

Of seventy-three cases thus charted, forty-one, or 56 per cent., showed an increase in sinus arrhythmia as the respiratory response increased in the earlier portion of the test. This increase in the degree of the sinus arrhythmia continued while the heart was accelerating moderately, but as the pulse accelerated more markedly in the latter part of the test, the degree of sinus arrhythmia decreased to about its

TABLE 2.—PULSE RATE AND THE DEGREE OF SINUS ARRHYTHMIA IN THE PRELIMINARY TRACING, AT FIVE MINUTE INTERVALS DURING THE TEST, AT THE POINT OF TERMINATION OF THE TEST, AND IN THE RECOVERY PERIOD

No	Age	O %	Rate								Sinus Arrhythmia										Time	
			P1	7	12	17	22	27	32	T	R	Pr	7	12	17	22	27	32	T	R		
32	30	10.4	52	54	56	58	56	54	...	51	50	25	35	30	15	20	25	...	35	40	29:20	
33	21	7.8	80	88	90	90	90	89	...	110	84	30	25	15	10	10	10	...	05	20	31	
34	22	6.7	90	78	88	92	100	102	108	130	68	25	20	25	15	10	05	00	00	40	31:48	
35	26	9.2	66	74	...	70	82	81	...	93	80	30	25	...	20	20	...	...	10	30		
36	23	7.8	50	64	...	64	74	84	...	90	56	35	40	...	40	30	20	...	10	40	30:15	
37	24	6.2	74	76	80	82	87	96	108	128	75	20	25	60	35	20	10	...	05	40	34:05	
38	...	7.3	64	72	66	69	81	94	...	...	74	20	25	25	15	10	00	...	00	35	27:05	
39	23	9.0	70	81	82	78	70	...	80	84	70	15	10	10	05	25	...	30	05	25	35:03	
40	40	5.8	63	88	90	82	88	84	110	110	84	25	20	15	20	16	10	00	00	20	32	
41	27	8.9	78	86	90	80	98	...	...	...	75	30	30	20	25	10	...	...	...	...		
42	34	13.1	86	88	90	...	...	...	...	90	90	10	10	00	...	...	...	00	10	17		
43	31	11.6	60	66	...	70	...	...	...	60	60	25	20	...	20	...	...	20	20	...		
44	25	9.7	72	72	78	78	84	90	...	75	10	25	20	35	2	05	...	...	30	27:30		
45	21	8.7	96	102	92	98	100	110	...	108	78	30	30	40	30	20	10	...	10	30	31	
46	24	7.3	98	108	106	108	...	...	...	...	80	20	10	10	05	...	...	...	20	25		
47	22	6.2	84	78	81	78	96	...	...	96	66	10	10	10	30	10	...	10	20	29		
48	24	6.8	86	78	84	96	102	120	...	...	88	25	10	20	10	05	...	...	20	27		
49	...	...	60	63	64	66	86	96	...	116	66	50	30	30	25	35	40	...	10	45		
50	...	...	62	63	64	68	72	82	...	90	62	40	45	40	45	35	25	...	20	30		
51	...	...	58	60	62	66	69	...	...	70	60	15	20	20	10	10	...	...	00	15	26:15	
52	...	...	84	84	84	96	99	117	...	117	108	10	20	20	05	05	00	...	00	00	27	
53	...	...	68	68	72	72	84	...	...	100	60	45	55	60	60	30	...	10	50	25:20		
54	...	...	68	70	72	76	88	...	...	88	56	40	40	30	20	05	...	05	60	...		
55	...	...	66	68	70	72	75	87	...	132	69	20	30	20	20	20	20	...	00	45	36:26	
56	...	...	66	72	69	78	...	...	...	...	94	66	25	30	30	25	25	10	...	10	45	28:15
57	...	...	68	72	72	80	82	94	...	94	66	20	20	20	20	15	10	...	00	20	26:53	
58	...	...	88	94	94	111	114	...	...	132	102	20	20	20	15	10	...	00	20	26:55		
59	...	...	66	74	78	88	94	...	...	114	66	10	40	35	20	25	...	15	40	26:55		
60	...	...	64	68	75	80	84	84	96	96	78	10	10	10	20	20	20	20	20	32		
61	...	...	102	90	102	100	114	114	126	126	96	20	20	20	15	15	10	00	00	20	32:25	
62	...	...	70	76	76	76	84	93	...	93	66	30	30	20	20	20	10	...	05	20	30	
63	...	...	70	72	72	74	78	96	...	96	60	20	20	20	20	15	15	...	10	20	29	
64	...	...	72	84	84	90	94	90	...	90	66	15	30	20	20	20	20	...	20	30	34	
65	...	...	84	72	72	84	...	...	...	72	30	20	20	10	...	...	...	...	10	21		
66	...	...	90	84	94	...	...	...	...	...	90	20	...	20	15	...	...	...	...	22		
67	...	...	84	90	...	90	96	102	...	102	72	10	20	...	25	10	00	...	00	30	27	
68	...	...	80	82	84	90	102	...	...	...	78	20	20	20	20	10	...	...	20	29:40		
69	...	...	104	102	...	116	...	...	...	...	...	15	20	...	20	...	...	...	...	...		
70	...	...	66	...	...	84	...	...	...	102	84	25	...	...	...	10	...	...	10	35		
71	...	...	96	96	100	96	108	114	126	...	102	15	15	15	10	10	05	00	...	10	32:23	
72	...	...	78	90	90	90	84	...	...	102	96	30	20	20	20	25	...	05	20	26:34		
73	...	...	78	92	96	86	94	108	120	126	...	20	25	25	25	15	10	05	05	...		
74	...	...	96	84	93	90	102	...	...	...	90	20	20	20	20	10	...	...	30	30	29:37	
75	...	...	78	72	72	84	88	78	102	102	72	20	30	30	35	35	10	...	10	30		

TABLE 3.—PREMATURE VENTRICULAR CONTRACTIONS

	Time, Minutes	Percentage Premature Ventricular Contractions	Pulse Rate		Time, Minutes	Percentage Premature Ventricular Contractions	Pulse Rate
Lt. N.	Pr	2	70	Lt. L.	Pr	11.1	57
	5	0	71		5	12	70
	10	4	70		10	11.6	68
	18	2	78		15	12.7	68
	24	1	82		20	9.8	75
	28	2	88		25	12	90
	30	6	98		30	0	102
	Off	0	—		Off	—	—
Sgt. S.	32	0	54	Sgt. W.	33	9	56
	Pr	9.4	61		Pr	4.6	74
	6.36	0	66		3	50	84
	8	1.7	65		7	50	84
	12	1.7	80		10	50	90
	18	0	80		18	15.5	86
	22	0	92		24	41.6	88
	25	0	102		27	21.6	93
	27	0	108		28	0	102
	Off	—	—		29	20.5	98
	32	—	72				

initial value or less. There was no fixed rate at which this decrease began, and in different individuals it was found at different rates between 62 and 96.

In fifteen cases there was a decrease in the degree of sinus arrhythmia on the commencement of the test, and a further decrease in degree as the test progressed and the rate accelerated. In fourteen cases there was no change in the degree of the sinus arrhythmia until the pulse accelerated in the latter part of the test, when the degree decreased. In two cases there was an increase in the degree of sinus arrhythmia in the first part of the test, then no further change. In one of these, Case 12, the increase was slight, and the pulse did not accelerate beyond a rate of 75. The other, Case 74, also showed a slight increase in the degree of sinus arrhythmia, with a rapid pulse rate throughout the test, beginning at 104 and finishing the test with a rate of 116. One case only showed no change in the degree of sinus arrhythmia at all, Case 45, but in this case the pulse rate did not accelerate over 70 at any time during the test.

In general, then, sinus arrhythmia showed a tendency to increase as the respiratory response increased, due, presumably, to effects operating on the vagal mechanism. This was followed by a decrease in the degree of sinus arrhythmia as the pulse accelerated in the latter part of the test. In some instances, observed during the routine examination of aviators, before the present series was run, cases of sinus arrhythmia were seen so marked as to present a very irregular pulse, where the respiratory phases were difficult or impossible to detect, and where there was a possibility of confusion with a more serious arrhythmia. In all of these cases the arrhythmia improved or disappeared as higher altitudes were reached and the pulse rate accelerated.

The appearance and character of the sinus arrhythmia was checked against the altitude reached, the minute volume of respiration, respiratory irregularities, and the depth of respiration, but all without any apparent correlation.

#### PREMATURE VENTRICULAR CONTRACTIONS

Premature ventricular contractions were observed in only two aviators before taking the rebreather test, out of a total of seventy-eight on whom graphic records were obtained with the polygraph, or about 2.6 per cent. Both were normal men without any demonstrable cardiac pathology, and each made a normal response to lowered oxygen tension. Four others showed one or more premature contractions during the test. In addition three men from the laboratory personnel who were known to have frequent premature ventricular contractions volunteered to take the test. Of the aviators who developed premature ventricular contractions during the test, one showed one such beat only

after 12 minutes, with a pulse of 64, one at 12 minutes, with a pulse rate of 90, and one interpolated beat after the conclusion of the test, with a pulse rate of 84. The other subject showed one premature ventricular contraction beat at 12 minutes, with a rate of 66, one at 17 minutes with a rate of 69, and one at 20 minutes with a rate of 76. The pulse accelerated to 94 with no further ectopic beats.

The other cases are best shown in the accompanying tables. The preliminary tracing before the test is indicated by "Pr," and the time at which the tracing was taken when the premature ventricular contractions were observed is indicated. The incidence of the premature ventricular contractions is expressed as the percentage of the total number of beats for the period observed. "Off" indicates the termination of the test, after which another tracing was taken during the recovery period.

Sgt. W. was the only case showing any cardiac pathology. He gave a history of tonsillitis yearly, usually two or three attacks each year, until April, 1918, when a tonsillectomy was performed while in the army. Since this time he has felt much better, and has gained 15 pounds in weight. He had influenza in France in December, 1918. He has had at no time any symptoms referable to the heart. The heart was found to be slightly enlarged on physical examination. There was a presystolic thrill and murmur at the apex, with an accentuated mitral first tone, and an accentuated pulmonic second. Extra systoles were present at examination for entrance into the army, and later while in service he was referred to a special board because of them, but was passed for duty. In this case the premature ventricular systoles reappeared at 28.40, and were still present at 29.30, when the test was terminated by unconsciousness.

Capt. O., of the laboratory personnel, showed 2.2 per cent. of premature ventricular contractions in the preliminary tracing before the test, at a rate of 60. At all times when previously examined he had shown the same ectopic beats in varying degrees of frequency. With the beginning of the test they disappeared at a rate of 75, and only one such beat was found during the test, at 8 minutes at a rate of 84. We had a similar experience with Capt. O. during a test in an electrocardiographic series yet to be reported.

From the cases shown it will be observed that there is a tendency for the incidence of the premature ventricular contractions to increase as the test progresses and the respiratory response increases but only in the earlier periods of the test. As the pulse accelerates the incidence decreases and they finally disappear. The exception is Sgt. W. in whose case there was reason to assume a pathologic basis.



In a series of several hundred cases given the official low oxygen test from Oct. 4, 1918 to May 7, 1919, where one of us either examined the cases personally, or was in immediate touch with the examination through his associates, no case of ectopic beats was observed in which the extra-systoles did not disappear before the termination of the rebreather test.

It is not felt that premature ventricular contractions are of themselves of pathologic significance. They tend to disappear as the heart responds in rate to the increased demands upon it, and as the non-refractory period is reduced by this increase in rate, as in exercise. Premature ventricular contractions should not of themselves be a basis for rejection in examinations for a flying status, or used as a basis for a lowered rating in the classification. That such extra-systoles have little influence in reducing the mechanical efficiency of the heart has been recently shown experimentally by Eyster and Swarthout.<sup>7</sup>

#### PULSUS ALTERNANS

Pulsus alternans was watched for with especial care, and more particularly just before the test was terminated because of impending unconsciousness, when there might be reason to expect that the heart rate was out of proportion to its strength. In one case a few alternating beats were observed at a rate of 95. The difference in height of the waves is very slight, as shown in Figure 8. One other case was observed.

The physiologist taking the blood pressure at one minute intervals in all of the routine cases examined had an excellent opportunity to detect alternation of the pulse. The fact that cases have not been observed at any time in taking the pulse and systolic pressure would indicate that it is a rare phenomenon at best.

We wish to make acknowledgement to Lieut.-Col. L. H. Bauer, officer in charge of the Medical Research Laboratory, and to our colleagues of the laboratory for cooperation and assistance.

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7. Eyster, J. A. E., and Swarthout, E. C.: *Arch. Int. Med.* **25**:317 (March) 1920.

# THE USE OF A HIGH FAT DIET IN THE TREATMENT OF DIABETES MELLITUS \*

## SECOND PAPER: BLOOD SUGAR

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In a previous communication<sup>1</sup> we discussed in outline the advantages of the use of a high fat diet in the treatment of diabetes mellitus. We reported briefly the results of an investigation of the effect of a diet whose energy came largely from fat, to which was added sufficient protein to maintain nitrogen balance and the minimal carbohydrate necessitated in making up a diet that a human being can eat over a long period of time. It was shown that with such a diet, glycosuria was avoided in severe diabetics, and that acidosis was not produced.

The first paper stated the method employed and, in a general way, the results obtained. Freedom from glycosuria, however, does not necessarily mean normal glycemia. In this communication we shall deal with the effect of this type of diet on the blood sugar.

Blood sugar determinations, sufficiently numerous to permit drawing conclusions concerning the effect of the diet on glycemia, are available in forty-five cases. We include in this group every case in which such a series of determinations has been made, and have omitted only those whose blood sugar determinations have been too few to be of significance. A few patients left the hospital on higher diets than those shown in the tables, but as corresponding blood sugar determinations are not available, the tables for such individuals stop with the last blood sugar reading.

These cases are presented in four groups. The first three groups (Tables 1, 2 and 3), consisting of forty cases, show a satisfactory response of the blood sugar to the treatment. The fourth group (Table 4) comprises the five cases in which blood sugars did not reach a desirably low percentage. Of the forty satisfactory cases, those complicated by chronic nephritis have been brought together in Table 2, and those in which diets varied at times from our standard are presented in Table 3.

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\* From the Department of Internal Medicine, Medical School, University of Michigan.

1. Newburgh, L. H., and Marsh, P. L.: The Use of a High Fat Diet in the Treatment of Diabetes Mellitus: First Paper, *Arch. Int. Med.* **26**:657 (July) 1920.

TABLE 1.—CASES SHOWING SATISFACTORY RESPONSE OF BLOOD SUGAR  
TO TREATMENT

No.	Case	Day	Blood Sugar per Cent.	Pro- tein, Gm.	Fat, Gm.	Car- bohy- drate, Gm.	Calories	Remarks
1	19-391 Male 47 Osteomyelitis of foot 144 lbs.	1	.....	16	100	10	1,000	
		3	0.082					
		6	0.060					
		8	0.070					
		9	.....	30	128	10	1,370	
		11	0.130					
		14	0.109					
		16	.....	40	225	13	2,350	
		19	0.100	54	240	13	2,400	
		21	0.100					
		23	0.120					
2	19-537 Male 21 127 lbs.	1	0.300	22	110	10	1,200	
		5	0.211					
		7	0.400					
		9	0.176					
		12	.....	29	135	8	1,475	
		20	0.175					
		27	.....	38	135	8	1,500	
		31	0.140					
		36	.....	15	42	10	500	
		40	0.176					
		43	.....	29	175	8	1,475	
		45	0.187					
		55	0.125					
		59	.....	30	165	8	1,700	
		62	0.146					
		69	0.111					
3	19-567 Male 49 153 lbs.	1	0.310	16	100	10	1,000	
		11	0.120					
		12	0.080					
		16	0.170					
		17	.....	65	200	10	2,100	
		20	0.095					
		23	0.075					
		27	0.100					
		32	0.090					
		43	0.070					
4	19-264 Female 66 144 lbs.	1	0.325	16	95	10	960	
		5	0.130					
		6	0.120	19	140	10	1,400	
		13	0.150	40	140	10	1,500	
		29	0.210					50 gm. bread added to diet one day; glycosuria
		33	0.140					
		37	0.110					
		45	0.100					
5	19-108 Male, 54 Chronic myocarditis 162 lbs.	1	0.200	16	95	10	960	
		3	0.107	23	140	10	1,425	
		5	0.100					
		6	.....	29	152	10	1,550	
		8	0.107					
		10	0.125					
		16	.....	60	115	40	1,450	
		18	0.075					
		38	0.100					
6	19-295 Male 53 160 lbs.	1	0.55	16	95	10	960	
		4	0.14					
		6	0.19	9	155	31	1,600	
		12	0.235					
		14	.....	..	..	..	.....	Starvation 24 hours
		15	0.14	16	100	13	1,025	
		20	0.17					
		28	0.083					
		30	.....	..	..	..	.....	Left hospital and did not adhere strictly to diet
		43	0.25	16	100	13	1,025	
		45	0.09					
		50	0.107					
		52	0.09					
		53	0.075					
		55	.....	18	125	7	1,150	
		57	0.065	34	160	8	1,600	
		62	.....	34	170	7	1,700	
		70	0.100					

TABLE 1.—CASES SHOWING SATISFACTORY RESPONSE OF BLOOD SUGAR  
TO TREATMENT—(Continued)

No.	Case	Day	Blood Sugar per Cent.	Pro- tein, Gm.	Fat, Gm.	Car- bohy- drate, Gm.	Calories	Remarks
7	19-306 Male 66 Osteomyelitis of foot 144 lbs.	1	0.550	19	97	10	980	
		7	0.200					
		10	0.110					
		13	.....	25	140	10	1,300	
		17	0.09					
		23	0.190					
		24	0.187	19	97	10	980	
		28	0.140					
		33	0.100	16	108	10	1,000	
		34	0.140					
		35	.....	36	220	11	2,230	
		38	0.150					
		42	.....	42	247	15	2,400	
		44	0.110	47	257	12	2,660	
8	19-467 Female 52 181 lbs.	49	0.100					
		50	.....	100	250	13	2,800	
		58	0.100					
		1	.....	16	100	13	1,000	
		7	0.15	23	140	10	1,400	
		12	0.15					
9	20-1 Male 60 174 lbs.	16	0.13	30	217	11	2,100	
		28	0.14					
		..	.....	..	..	..	.....	Diet had been re- stricted previous to entrance for opera- tion for cataracts
		1	0.19	16	100	10	1,000	
10	19-130 Male, 31 124 lbs.	5	0.15					
		10	0.10					
		1	0.225	16	100	10	1,000	
11	20-458 Male, 65 121 lbs.	6	0.190					
		8	0.145	..	..	..	.....	Left against advice
		1	0.18	27	130	12	1,350	
12	20-660 Female 60 114 lbs.	7	0.13					Unexplained bema- turia; refused cyst- oscopy and left
		1	0.35	18	90	14	950	
		8	.....	28	130	20	1,400	
		9	0.11					
		13	0.10					
		17	..	34	170	27	1,800	
		18	0.10					
		19	.....	55	110	85	2,200	
		30	0.14	..	..	..	.....	30 min. after meal
13	19-355 Female 66 138 lbs.	1	0.33	19	90	10	925	
		3	0.30					
		6	0.153					
		8	.....	32	145	14	1,500	
		9	0.136					
		11	0.125	38	200	11	2,000	
		15	0.270	..	..	..	.....	Dietetic error
		17	0.136					
14	20-376 Female, 55 135 lbs.	1	0.24	15	100	12	1,000	
		6	0.17					
		9	0.11					
15	19-261 Female 61 151 lbs.	1	0.450	16	95	10	960	
		7	0.125					
		9	0.160	16	140	10	1,400	
		13	0.145	..	..	..	.....	7:00 p. m.
16	21-51 Male 73	1	0.17	16	95	10	960	
		5	0.136	50	235	28	2,400	
		8	0.130					
17	19-163 Male 75 151 lbs.	1	0.275	15	100	10	1,000	
		4	0.145					
		5	.....	55	135	10	1,450	
		6	0.130					
		7	..	65	150	10	1,650	
		9	0.180	..	..	..	.....	Ate candy
		11	0.160					
		17	0.140	45	110	30	2,200	
18	20-753 Female 53 180 lbs.	41	0.130					
		1	0.30	16	90	14	900	
		4	0.18					
		5	.....	25	135	20	1,400	
		6	.....	30	180	25	1,800	
		7	.....	55	230	30	2,400	
		8	0.13					
		9	0.10					

TABLE 1.—CASES SHOWING SATISFACTORY RESPONSE OF BLOOD SUGAR  
TO TREATMENT—(Continued)

No.	Case	Day	Blood Sugar per Cent.	Pro- tein, Gm.	Fat, Gm.	Car- bohy- drate, Gm.	Calories	Remarks
19	20-759	1	0.35	16	90	14	900	
	Male	4	0.21					
	48	8	0.14					
	162 lbs.	19	0.11					
20	20-558	1	0.37	16	90	14	900	
	Male	5	0.12					
	35	15	.....	25	135	20	1,400	
	152 lbs.	17	.....	30	180	25	1,800	
		23	0.07					
21	20-653	1	0.16	16	90	14	900	
	Male	3	0.10					
	22	7	0.11					
	Restricted	10	.....	30	180	25	1,800	
	before	13	0.08					
	entrance	15	.....	55	230	30	2,400	
	118 lbs	17	0.11					
		22	0.08					
		31	0.14					
		41	0.07					
		43	0.13					
		114	0.12					
22	20-882	1	0.30	16	90	14	900	
	Male	5	0.19					
	63	13	0.18					
	141 lbs.	16	.....	25	135	20	1,400	
		18	0.16	30	180	25	1,800	
		25	0.11					
23	20-738	1	.....	16	90	14	900	
	Female	3	0.19					
	56	4	0.20					
	131 lbs.	6	.....	25	135	20	1,400	
		8	0.09	30	180	25	1,800	
24	20-703	1	.....	16	90	14	900	
	Male	3	0.18					
	46	5	0.17					
	168 lbs.	7	.....	25	135	20	1,400	
		9	0.09	30	180	25	1,800	
		12	.....	55	230	30	2,400	
		15	0.06					
25	20-688	1	.....	16	90	14	900	
	Male	2	0.15					
	68	4	.....	25	135	14	1,400	
	153 lbs.	5	0.12					
26	21-8	1	.....	16	90	14	900	
	Male	3	0.267					
	33	4	0.220					
	128 lbs.	5	0.120					
		9	0.180					
		11	.....	25	135	20	1,400	Dietetic error
		13	0.120					
		15	0.130					
		18	0.180					
		22	0.150					Drank 2 glasses milk without permission
		27	0.120					
27	21-9	1	0.230	16	90	14	900	
	Female	4	0.120	25	135	20	1,400	
	18	5	.....					Menstruation
	155 lbs.	8	0.420					
		10	0.17					
		14	0.15					
		17	.....	30	180	25	1,900	
		19	0.14	45	180	10	1,900	
		23	0.13					
28	21-31	1	0.27	16	90	14	900	
	Female	5	0.125	25	135	20	1,400	
	67	8	0.16	30	180	25	1,800	
	168 lbs.	12	0.12					

The twenty-eight cases contained in Table 1 show that a high fat diet such as we have used is capable of bringing the blood sugar down to normal and keeping it at that level during the period of observation.

TABLE 2.—RESPONSE TO TREATMENT OF BLOOD SUGAR IN DIABETICS WITH MARKED NEPHRITIS

No.	Case	Day	Blood Sugar per Cent.	Pro- tein, Gm.	Fat, Gm.	Car- bohy- drate, Gm.	Calories	Remarks
29	19-371	1	0.205	16	100	10	1,000	
	Male	3	0.115					
	47	7	0.092					
	158 lbs.	8	0.136	60	150	10	1,700	
		15	0.130					
30	19-438	1	.....	16	95	10	960	
	Female	2	0.190					
	60	8	0.180					
	217 lbs.	12	0.125	25	150	10	1,500	
		13	.....					
		18	0.200					
		19	0.185					
		22	0.200					
		23	.....	30	205	10	2,000	
		26	0.125					
		27	0.130					
31	19-218	1	0.380	16	95	10	960	
	Female	3	0.232					
	68	8	0.150					
	156 lbs.	9	.....	45	160	12	1,700	
		10	0.150					
		17	0.140					
		21	0.140					
		27	0.135					
		27	0.100					
32	19-56	1	0.18	16	95	10	960	
	Female	3	.....	42	130	10	1,400	
	56	7	0.11					
	168 lbs.	9	0.12	..	...	..	...	25 gm. bread added later caused glyco- suria
33	19-131	1	0.30	16	95	10	960	
	Female	5	.....	42	135	10	1,300	
	60	7	0.145	60	155	10	1,700	
	131 lbs.	10	0.145					
		13	0.125					
34	19-84	1	0.425	16	95	10	960	
	Female, 51	6	0.115	40	110	10	1,200	
	175 lbs.	7	0.120					
35	21-19	1	0.30	16	95	14	950	
	Male	5	0.15					
	76	6	.....	25	135	20	1,400	
	133 lbs.	9	0.22					
		10	0.20	30	180	25	1,600	
		14	...	35	230	30	2,400	
		18	0.18					
		28	0.125					

The seven cases presented in Table 2 are separated from the rest because of the well known fact that chronic nephritis in diabetics tends to keep the blood sugar at an abnormally high level.<sup>2</sup> These patients

2. Meyers, V. C., and Bailey, C. V.: The Lewis and Benedict Method for the Estimation of Blood Sugar, with Some Observations Obtained in Disease, *J. Biol. Chem.* **24**:147, 1916. Bing, H. J., and Jakolson, B.: Blutuntersuchungen unter normalen u. einigen pathologische Verhältnissen, *Deutsch. Arch. f. klin. Med.* **113**:571, 1914. Hopkins, A. R.: Studies in the Concentration of Blood Sugar in Health and Disease as Determined by Bang's Micromethod, *Am. J. Med. Sc.* **149**:254, 1915.

all had a severe nephritis as shown by decreased output of phenolsulphonephthalein, hypertension, high blood urea and the persistence of albumin and casts in the urine days after the disappearance of the glycosuria. It is of special interest to note that the blood sugar of each of these individuals is brought to a point well within normal limits.

The six cases in Table 3 show well the occurrence of hyperglycemia resulting from diets high in protein and the reduction of the blood sugar

TABLE 3.—PATIENTS TREATED BY VARYING REGIMÉS

No.	Case	Day	Blood Sugar per Cent.	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories	Remarks
36	18-382	1	.....	200	135	..	2,075	"Von Noorden" diet
	Male	3	0.275					
	30	6	0.215					
	118 lbs.	8	.....	16	100	10	1,000	High fat diet
		14	.....	52	220	10	2,225	
		17	0.127					
		18	.....	62	315	10	3,100	
		20	0.155					
		30	0.113					
37	18-613	1	.....	200	135	..	2,075	"Von Noorden" diet
	Female	9	0.400					
	35	10	.....	16	100	10	1,000	High fat diet
	117 lbs.	12	0.230					
		13	.....	30	135	10	1,400	
		16	0.166					
38	18-657	1	.....	200	135	..	2,075	"Von Noorden" diet
	Female	2	0.214	16	100	10	1,000	High fat diet
	46	6	.....	42	155	10	1,600	
		10	0.130					
		12	.....	200	135	..	2,075	"Von Noorden" diet
		13	0.200					
		16	0.200					
39	19-165	1	0.273	16	95	10	960	The excess of protein caused a hyperglycemia
	Male	3	0.145					
	75	4	.....	45	160	12	1,700	
	180 lbs.	5	0.130					
		6	.....	70	160	12	1,800	
		7	0.180					
		9	0.160					
		15	0.140					
40	19-56	1	0.500	16	95	10	960	Urine sugar free after the fifth day
	Female	7	.....	22	100	10	1,025	
	53	8	.....	34	110	10	1,150	
	168 lbs.	11	.....	37	130	23	1,400	
		13	0.135					
		14	.....	50	120	22	1,375	
		15	0.195					
		16	.....	37	130	23	1,400	
		18	0.130	50	120	22	1,375	
		19	0.190	50	120	35	1,500	
		23	0.170					
		24	0.185					

to within normal limits subsequent to the use of a diet low in protein and high in fat. Case 40 is especially instructive in this respect. After four days on a diet containing 37 gm. protein and 1,400 calories, the blood sugar was 0.135 per cent.; after an increase of the protein to 50 gm., with a slight decrease in carbohydrate and total calories, a hyperglycemia of 0.195 per cent. is noted. A return to the former diet

brought the blood sugar down to 0.130 per cent. while the substitution of the second diet again produced a hyperglycemia of 0.190 per cent.

The five cases in Table 4 are those in which response to treatment was not satisfactory. Two of these (Cases 42 and 45) had severe

TABLE 4.—PATIENTS NOT RESPONDING SATISFACTORILY TO TREATMENT

No.	Case	Day	Blood Sugar per Cent.	Pro- tein, Gm.	Fat, Gm.	Car- bohy- drate, Gm.	Calories	Remarks	
41	19-440	1	0.52	16	97	10	1,000		
	Male	4	0.36						
	18	6	0.29						
	90 lbs.	8	0.24						
		11	0.20						
		12	.....	..	...	..	.....	Broke diet	
		13	0.42						
		18	0.23						
		21	0.15						
		26	.....	25	140	10	1,400		
		28	0.16						
		33	0.15	..	...	..	.....	Patient in N bal- ance; left the hos- pital in excellent condition	
		38	0.13	37	190	10	1,900		
		39	0.15						
		41	0.18						
		50	0.15						
	42	19-229	1	0.375	16	95	10	960	Far advanced squa- mous cell carci- noma of uterus
Female		5	0.187						
54		6	0.166				.....	Discharged against advice	
120 lbs.		7	0.215	..	...	..	.....		
43		20-423	1	.....	16	100	10	1,000	
		Male	4	0.20					
		63	9	0.16					
		81 lbs.	15	.....	28	140	30	1,400	
		23	0.15						
44	19-265	1	0.400	16	95	10	960		
	Male	6	0.120						
	61	7	.....	16	130	10	1,300		
	149 lbs.	11	0.120						
		12	0.275	..	...	..	.....	Urine sugar free	
		15	.....	30	200	21	2,000		
		21	0.225	..	...	..	.....	Urine sugar free	
		27	.....	9	155	31	1,600		
		29	0.150	..	...	..	.....	Left hosp. against advice	
		34	0.200						
	45	20-311	1	0.400	16	100	10	1,000	Cerebro-spinal syph- ilis
Male		3	0.135						
40		7	0.160						
124 lbs.		8	.....	21	156	11	1,500		
		9	0.125						
		15	0.140						
		18	.....	48	240	15	2,500		
		20	0.170						
		29	0.160						

complicating diseases. We suspected but could not prove that one patient (Case 44) was not adhering to his diet; we can give no other explanation for the rise in his blood sugar from 0.120 to 0.275 per cent. between the eleventh and thirteenth days, in the absence of any change in diet on our part.



NEW METHODS FOR ESTIMATING ENZYMATIC  
ACTIVITIES OF DUODENAL CONTENTS  
OF NORMAL MAN \*

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In a former paper<sup>1</sup> reference was made to the need of data concerning details of the physiology of the human gastrointestinal tract in order that experimental observations on the functional pathology of the latter might be more intelligently interpreted. The present communication is a continuation of physiologic investigation of the alimentary canal in normal man, and deals with methods for the study of the enzymatic activities of the duodenal contents.

A résumé of most of the methods which have been used for such studies in the past is given in the appendix of the book of Euler.<sup>2</sup> The methods, or their modifications, which have been used most frequently in investigation in clinical medicine are as follows:

*Proteolytic enzymes.*—Methods of Gross<sup>3</sup> and Mett.<sup>4</sup> The method of Gross is a modification of one devised by Volhard.<sup>5</sup> It is based on the principle that from faintly alkaline solutions (0.1 per cent. sodium carbonate) casein is precipitated by dilute acids (0.1 per cent. acetic acid), while the digestion products remain in solution. More recently this method was modified by Spencer.<sup>6</sup> The Mett method is the well known one of measuring the lengths of coagulated egg albumin in capillary glass tubes before and after placing them into a solution of an enzyme. This method has been modified by Einhorn.<sup>7</sup>

*Lipolytic enzyme.*—Ethyl butyrate method. This method is based on the development of butyric acid by lipase and the determination of the acidity developed by titration with tenth normal sodium hydroxid.

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\* From the medical clinic and radiographic department of the Peter Bent Brigham Hospital.

1. McClure, C. W.; Reynolds, L., and Schwarz, C. O.: Arch. Int. Med. **26**: 410 (Sept.) 1920.

2. Euler, H.: General Chemistry of the Enzymes, Translated by T. H. Pope, New York, 1912.

3. Gross, O.: Arch. f. exper. Pathol. u. Pharmakol. **58**:157, 1907; Deutsch. med. Wchnschr. **35**:1706, 1909.

4. Mett: Loc. cit., Footnote 2.

5. Volhard, F.: Munchen. med. Wchnschr. **54**:403, 1907.

6. Spencer, W. H.: J. Biol. Chem. **21**:165, 1915.

7. Einhorn, M.: Med. Rec. **82**:650, 905, 1912.

*Amylolytic enzymes.*—Method of Wohlgemuth.<sup>8</sup> The Wohlgemuth method is based on the production of erythro-dextrin in starch solution (alkaline with sodium carbonate). The presence of erythro-dextrin is determined by the color produced on the addition of a solution of iodine.

All methods which have been applied to the estimation of the enzymatic activities of the duodenal contents are open to serious criticism, which will be discussed later. Under these circumstances it was deemed necessary to devise new methods. Methods have finally been devised which combine delicacy, uniformity and proportionality of enzymatic activity and accuracy of estimation of the amount of enzyme action. Uniformity and proportionality of enzymatic activity have been obtained by regulating the latter with phosphate mixtures. The amount of enzyme action for the proteolytic and amylolytic enzymes is estimated by application of the methods of Folin and Wu<sup>9</sup> for the determination of nonprotein nitrogen, with the modification that metaphosphoric acid is used as the protein precipitant, and of sugar in the blood. The activity of fat splitting enzyme is estimated by determining the degree of acidity developed in a true emulsion of cotton seed oil, by titrating while hot with alcoholic potash solution, using phenolphthalein as an indicator.

#### ESTIMATION OF PROTEOLYTIC ACTIVITY OF DUODENAL CONTENTS

##### REAGENTS

*Phosphate mixture.*—Two-tenths molar phosphate mixture of  $p_{\text{H}}$  8.4 is prepared as follows: add 20 c.c. of a solution of potassium acid phosphate [ $\text{KH}_2\text{PO}_4$ ] (C.P.), containing 27.234 gm. to the liter, to 980 c.c. of a solution of disodium phosphate [ $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ ]<sup>10</sup> (C.P.), containing 35.628 gm. to a liter.

*Casein solution.*—Neutralize 1 gm. (accurate weight) of soluble casein<sup>11</sup> with 4 c.c. of tenth normal sodium hydroxide solution and add 100 c.c. of the 0.2 molar phosphate mixture. By the aid of heat and vigorous rotation of the flask dissolve the casein completely. This is

8. Wohlgemuth, J.: *Biochem. Ztschr.* **9**:1, 1908; *Berl. klin. Wchnschr.* **47**: 92, 1910.

9. Folin, O., and Wu, H.: *J. Biol. Chem.* **38**:81, 1919.

10. The usual C. P. preparations of disodium phosphate, obtainable on the market, contain twelve molecules of water ( $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ ). Such preparations should be thoroughly triturated in a mortar, and then air dried by spreading out on large filter papers in the open room. In from twelve to fourteen days the salt will lose ten molecules of water and then will be suitable for use as disodium phosphate ( $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ ). Phosphate mixtures containing the salt prepared in the manner described will give proper  $p_{\text{H}}$  as determined by the use of the potentiometer.

11. The preparation of casein used was one furnished by Dr. A. W. Bosworth, made according to the method devised by himself and L. L. Van Slyke, *Jour. Biol. Chem.* **14**:203, 1913.

done by adding the phosphate mixture to the casein in a dry flask and rotating quickly to prevent the formation of a doughy, relatively insoluble mass. The sodium hydroxid solution is then added and, continuing the rotation, the flask is heated over a small flame to 57 C., removed from the flame and rotated until the casein has dissolved.

*Twenty-five per cent. metaphosphoric acid solution.*<sup>12</sup> The preparation of metaphosphoric acid usually obtained on the market should be fused in a graphite mortar until the white fumes of phosphorus pentoxid begin to appear. The fused material can be cooled conveniently by pouring in a clean pie-pan floating on cold water. Metaphosphoric acid so fused will remain a potent protein precipitant if kept in tightly stoppered bottles. The 25 per cent. solution can be made quickly by triturating the desired amounts of metaphosphoric acid and water in a mortar.

*Digestion mixture and Nessler's solution* are prepared as directed by Folin and Wu,<sup>9</sup> the *standard ammonium sulphate solution* as directed by Folin and Denis.<sup>12</sup>

*Method.*—The duodenal contents are centrifuged until a clear or but slightly turbid supernatant fluid is obtained. The latter is decanted into a clean tube. In a 50 c.c. volumetric flask place 1 c.c. of this fluid and make up to the mark with 0.2 molar phosphate mixture solution of  $p_H$  8.4, and mix thoroughly.

Into test tubes (100x10 mm.) place 9 c.c. of the casein solution. Heat in the water bath at 40 C. for five minutes. Then add 1 c.c. of the diluted duodenal contents, mix and incubate in the water bath for thirty minutes at 40 C. Now add 2 c.c. of a freshly prepared 25 per cent. solution of metaphosphoric acid, mix thoroughly and filter. A perfectly clear, colorless filtrate should be obtained. One c.c. of this filtrate is added to 1 c.c. of the digestion mixture in a Pyrex glass tube (200x25 mm.), a quartz pebble is added and digestion is carried out according to the micro-Kjeldahl method of Folin and Wu for non-protein nitrogen in the blood. In brief, the method consists of boiling off the water and, when the white fumes of sulphuric acid begin to develop, the mouth of the tube is covered with a watch glass. Digestion is continued for from thirty to sixty seconds after the last trace of the brown color has disappeared. The tube is then allowed to cool for from sixty to seventy seconds, and from 5 to 10 c.c. of water are quickly added. The contents of the tube are cooled, made up to the 35 c.c. mark with water and 15 c.c. of Nessler's solution added. The nesslerized solution is centrifugalized to get rid of the sediment (the sediment must be pure white and not discolored by the precipitation of any of the coloring matter), and compared with standard ammonium

12. Folin, O., and Denis, W.: J. Biol. Chem., **26**:491, 1916.

sulphate solutions (usually containing 0.25 and 0.5 gm. nitrogen). These are prepared by placing 2 c.c. of the digestion mixture in a 100 c.c. volumetric flask, adding 5 or 10 c.c. of standard ammonium sulphate solution, about 60 c.c. of water, 30 c.c. of Nessler's solution and making up to the mark with water.

Two controls are probably necessary for safety: (1) 1 c.c. of the diluted duodenal contents and 9 c.c. of the 0.2 molar phosphate mixture solution; and (2) 9 c.c. of the casein solution plus 1 c.c. of the phosphate mixture. In our experience neither of the controls has developed more than a trace of yellow color after digestion and nesslerization.

TABLE 1.—AMOUNTS OF NON-PROTEIN NITROGEN DEVELOPED FROM CASEIN BY VARIOUS SAMPLES OF DUODENAL CONTENTS

No. of Sample	Amount of Diluted Duodenal Contents, C.c.	N Developed in Duplicate Analyses, Mg.
1	1.0	2.97
		2.99
2	1.0	3.52
		3.57
3	1.0	2.66
		2.63
4	1.0	1.51
		1.53
5	1.0	2.00
		2.03
6	1.0	1.47
		1.46
7	1.0	2.63
		2.60

#### ESTIMATION OF LIPOLYTIC ACTIVITY OF DUODENAL CONTENTS

##### REAGENTS

*Tenth Normal Sodium Hydroxid.* Made up in 95 per cent. ethyl alcohol.

*Fat emulsion.*—This is prepared by making a suspension of four parts of cotton seed oil, one part of powdered gum acacia and two parts of water according to the method given in the U. S. Pharmacopeia. Four hundred c.c. of this suspension are mixed with 600 c.c. of water and emulsified by running through a fat emulsifying machine at from 300 to 350 kilo pressure per square cm. The emulsion<sup>13</sup> may be put in pint milk bottles, hermetically sealed with patented metal caps and sterilized at 15 pounds pressure in the autoclave. Emulsion thus pre-

13. Emulsions were prepared for us by Dr. A. W. Bosworth of the Boston Floating Hospital.

pared keeps indefinitely. For use in digestion experiments the fat emulsion is mixed with an equal volume of the 0.33 molar phosphate mixture solution given below.

*Phosphate mixture solution.*—One-third (0.33) molar phosphate mixture solution of  $p_H$  8.4 is prepared as follows: 53.4425 gm. of disodium phosphate ( $Na_2HPO_4 \cdot 2H_2O$ ) are dissolved in exactly one liter of water; 20.4255 gm. of potassium acid phosphate ( $KH_2PO_4$ ) are dissolved in exactly 500 c.c. of water. Twenty c.c. of the potassium acid phosphate solution are added to 980 c.c. of the disodium phosphate solution which gives  $p_H$  8.4.

*Method.*—One c.c. of the centrifugalized duodenal contents are diluted to 50 c.c. with the 0.33 molar phosphate mixture solution. Nine c.c. of the fat emulsion phosphate mixture solution are pipetted into test tubes (100x10 mm.). The tubes are incubated in the water bath at 40 C. for five minutes; then 1 c.c. of the diluted duodenal contents

TABLE 2.—ACIDITY DEVELOPED IN COTTON SEED OIL EMULSION BY VARIOUS SAMPLES OF DUODENAL CONTENTS FROM A MAN

No. of Sample	Amount of Diluted Duodenal Contents, C.c.	Acidity Titrated with Tenth Normal Sodium Hydroxid in Duplicate Analyses
1	1.0	2.4 2.3
2	1.0	0.9 1.0
3	1.0	2.0 2.0
4	1.0	2.1 2.2

is added, the tubes shaken and again incubated for one hour at 40 C. Then the contents of the tubes are at once poured into small Erlenmeyer flasks (about 150 c.c. capacity), the tubes rinsed with about 20 c.c. of 95 per cent. ethyl alcohol and the rinsings added to the flasks (the ethyl alcohol has first been neutralized with tenth normal sodium hydroxid after adding phenolphthalein and titrating cold). Ten drops of a 1 per cent. phenolphthalein solution are added to each flask. The degree of acidity developed, due to the formation of fatty acids, is determined by titrating with tenth normal alcohol sodium hydroxid, with the contents of the flask boiling hot.

A control tube containing 9 c.c. of the fat emulsion phosphate mixture solution and one c.c. of the 0.33 molar phosphate mixture solution is to be used.

Under the experimental conditions outlined different samples from the same specimen of duodenal contents will develop acidities checking within 0.1 c.c. of tenth normal sodium hydroxid.

An example of the results obtained by the method are given in Table 2. The specimens of duodenal contents were obtained at intervals over a period of four hours from a healthy young man. All the specimens except No. 3 were taken from the second portion of the duodenum.

#### ESTIMATION OF AMYLOLYTIC ACTIVITY OF DUODENAL CONTENTS

##### REAGENTS

Molybdic acid reagent, copper sulphate mixture and the stock glucose solutions are prepared according to the direction given in the revised method of Folin and Wu,<sup>14</sup> for the estimation of sugar in the blood. The dilutions of the stock glucose solutions, which are to be used as standards, are made up in 0.1 molar phosphate solution of  $p_H$  8.4.

*Phosphate mixture solution.*—Two-tenths molar phosphate mixture of  $p_H$  8.4. This is prepared in the manner already described (proteolytic enzyme).

*Starch-phosphate mixture solution.*—Four gm. of soluble starch are completely dissolved in 100 c.c. of hot distilled water, cooled and diluted with an equal volume of the 0.2 molar phosphate mixture solution of  $p_H$  8.4.

*Method.*—In a 25 c.c. volumetric flask place 1 c.c. of the centrifuged duodenal contents, make up to the mark with the 0.2 molar phosphate mixture of  $p_H$  8.4 and mix thoroughly.

In test tubes (100x10 mm.) place 9 c.c. of the starch-phosphate mixture solution. Heat in the water bath at 40 C. for 5 minutes. Then add 1 c.c. of the diluted duodenal contents, mix and incubate in the water bath at 40 C. for 30 minutes. Incubation may be carried out for a period of one hour instead of the thirty minute period, if it is desirable to obtain a larger amount of starch digestion. In the meantime place 2 c.c. of the copper solution into the special blood sugar tubes of Folin and Wu.<sup>13</sup> After completion of the 30 minute incubation period pipet immediately 2 c.c. of the digested starch solution into the prepared blood sugar tubes, rotate the contents gently and place in boiling water for six minutes. Then cool, add 2 c.c. of the molybdate solution, make up to the mark, mix and compare the color produced with standard glucose solutions. These are prepared as follows: 2 c.c. of the standard glucose solution are added to 2 c.c. of the copper solution in the special blood sugar tubes, boiled along with the specimens for analysis and further treated the same as these specimens.

A control of 1 c.c. of the diluted duodenal contents and 9 c.c. of the starch-phosphate mixture solution should be used; 2 c.c. being imme-

14. Folin, O., and Wu, W.: J. Biol. Chem. **41**:367, 1920.

diately pipetted into the copper sulphate mixture to stop the action of amylolytic enzyme present.

Only preparations of soluble starch containing very small amounts of sugar should be used. It is convenient to determine the sugar content of a bulk of starch and then to use the preparation for all determinations. In this way the quantity of sugar present in the starch-phosphate mixture solution outlined in the method can be calculated. The amount present is to be deducted from the result obtained after the completion of digestion experiment.

Using the method outlined above, repeated estimations of the amylolytic activity of the same specimen of duodenal contents has always given the same result; that is, within the limits of experimental error.

TABLE 3.—SUGAR DEVELOPED FROM SOLUBLE STARCH BY VARIOUS SAMPLES OF DUODENAL CONTENTS FROM A MAN

No. of Sample	Amount of Diluted Duodenal Contents, C.c.	Mg. of Sugar Developed in Duplicate Analyses
2	1.0	1.43 1.43
3	1.0	0.79 0.76
4	1.0	1.41 1.41
5	1.0	2.07 2.07
6	1.0	0.76 0.75
7	1.0	0.97 0.97

Table 3 shows the results obtained in duplicate estimations of the amylolytic activities of various specimens of duodenal contents from a healthy young man.

#### DISCUSSION

If methods for estimating enzymatic activities of duodenal contents are to be used for clinical investigations, it is considered important that in devising such methods the following factors be given full consideration: (1) quantitative accuracy and practicability of procedures for estimating the amount of enzyme action; (2) uniformity of enzymatic activity; (3) proportionality of enzyme action; (4) stability of an enzyme; (5) physical state of the medium in which the enzyme is to act.

All methods previously proposed for the estimation of enzymatic activities of the duodenal contents are open to the poignant criticism that the five conditions enumerated were not fulfilled. In many of the methods for determining amylolytic and proteolytic activity the manner

of estimating the amount of digestion is not quantitatively accurate. In the majority of the methods the amount of duodenal contents required in the digestion experiments is so large that it greatly lessens the delicacy of the methods. The stability of the enzymes of the duodenal contents under the conditions present in many of the methods is unknown, but the experience of the authors makes it seem probable that it would be variable enough to interfere frequently with the uniformity of enzymatic action. This renders the accuracy of the results obtained by such methods questionable. Most of the methods for demonstrating lipolytic activity call for an initial neutralization with NaOH of the substance on which the enzyme is to act. In our experience this neutralization has frequently exerted a deleterious effect on the action of lipase present in duodenal contents.

During the action of enzymes in solution substances are formed which will change the hydrogen ion concentration of the solution, unless proper buffer conditions are present. The influence of the latter is discussed by Sörenson,<sup>15</sup> who points out that enzyme action is influenced as much by hydrogen ion concentration as it is by temperature. However, in none of the methods previously proposed for the estimation of enzymatic activity on duodenal contents was the effect of changes in hydrogen ion concentration on enzyme action considered. For this reason results obtained by these methods will be variable. In the methods here proposed such variability has been obviated by the use of proper molar and  $p_H$  of phosphate mixtures.

The five important conditions to be considered in methods for estimating enzymatic activity, outlined above, have been fulfilled in the new methods proposed. The manner in which this has been done is discussed as follows:

1. *Accuracy and practicability of the methods.*—The methods are practical inasmuch as the facilities for their performance are commonly present in clinical laboratories. The methods for determining the amounts of nitrogen and sugar developed are quantitatively accurate. But the difficulty in the titration of fatty acids is such that the method is open to a maximum error of 10 per cent.

2. *Uniformity of enzymatic activity.*—The action of an enzyme was considered uniform when, under a certain set of experimental conditions, the same results were obtained with a given specimen of duodenal contents on repeating analyses frequently over a period of the first twelve hours after the collection of the specimen. This criterion of uniformity of enzymatic activity has been met by regulating the latter with certain molar and  $p_H$  of solutions of phosphate mixtures described in the section outlining the methods.

15. Sörenson, S. P. L.: *Biochem. Ztschr.* **21**:301, 1909.



3. *Proportionality of enzymatic activity.*—By proportionality is meant the relation existing between the amounts of material digested by varying quantities of an enzyme containing solution. The principal conditions found which influenced proportionality were: buffer conditions and undetermined factors present in different specimens of duodenal contents. It was found that, unless the proper buffer conditions were present, the proportionality obtainable was often very slight. This held true for relatively large amounts of the solution containing the enzyme. Because of this it may be fairly inferred that any constancy in proportionality obtained by methods previously proposed must represent gross differences in the amounts of duodenal contents used.

The results obtained by the method proposed for the estimation of the activity of amylolytic enzyme have so far been found to be proportional. The proportionality shown by the results obtained for proteolytic activity in different specimens of duodenal contents has varied from 1:1.5 to 1:1.8, usually 1:1.6; for lipolytic activity from 1:1.5 to 1:2, usually the latter. Although the proportionality obtained by the use of different specimens of duodenal contents varied, for a given one it was constant.

There are chemical and physical variations in different specimens of duodenal contents, obtained either from the same or different persons, and it is probable that certain of these differences modify enzymatic activity, since the proportionality shown by the use of various specimens of duodenal contents differs. It may, therefore, readily be conceived that, although the enzymatic activity of given specimens of duodenal contents be made uniform, nevertheless, the proportionality might be generally so variable as to give deceptive results. There are two observations which make it appear as though such deception does not occur in the results obtained by the use of the methods proposed. In the first place, experience has demonstrated that the proportionality has fallen within the limits already given; and, secondly, under similar experimental conditions the methods proposed have given comparable results with thirty different specimens of duodenal contents from a series of normal persons.

4. *Stability of enzyme.*—Obviously, the stability of an enzyme in relation to the length of time its action is to be measured must be considered in any method for demonstrating uniformity or proportionality of enzymatic activity. This means that the action of the enzyme studied must be approximately as great at the conclusion of an experiment as it was at the beginning of the same. The criterion of stability followed in the experiments here presented has been constancy of both the uniformity and degree of proportionality obtained with the specimens of duodenal contents studied. Enzymatic activity of the latter

was observed over a period of the first twelve hours succeeding collection. During this time the activity of the three enzymes studied remained constant, as determined by the use of the methods here proposed. After dilution of the duodenal contents with the solution of the phosphate mixture lipolytic activity frequently diminished after about four hours, while the amylolytic and proteolytic activities remained unaffected a longer period. Nevertheless, it was considered advisable to use the duodenal contents as soon as diluted and then to discard the dilutions.

5. *Physical state of the medium.*—In order to obtain comparable results the physical conditions under which an enzyme acts must be constant. One essential reason for this is the fact that the size of the surface area of material exposed to enzyme action is a governing factor in the amount of the latter which will occur. In the methods proposed constant physical conditions, under which the enzymes act, have been obtained by means of solutions or true emulsions.

In the alimentary canal there is no apparent need for uniformity or proportionality of enzyme action. In vitro conditions are different and it is necessary to produce uniformity and proportionality of enzyme action in order to be able to show variations in the quality or quantity of the action of enzymes in different solutions. In the methods devised this has been brought about by conditions dissimilar to those present in the human intestinal tract. Furthermore, it should be emphasized that in these methods enzymatic activity, and not the amount of enzyme present, is measured.

## DERMATITIS AND ALLIED REACTIONS FOLLOWING THE ARSENICAL TREATMENT OF SYPHILIS \*

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The fact that physicians have frequently failed to appreciate the significance of dermatitis following the arsenical treatment of syphilis, or to differentiate the rashes of minor significance from those indicating grave constitutional disturbances, has prompted us to report the results of our study of a series of such cases of dermatitis and of allied reactions. Our experience has led us to believe that it is possible to divide all untoward reactions of this type into two classes from the viewpoint of their significance with regard to the continuation of arsenic therapy. We also believe that this study throws some light on the etiology, course and prognosis of these toxic phenomena, especially through the recognition of special factors underlying the constitutional disturbances in the graver type of reactions. We have, therefore, reviewed in some detail twenty-three cases of reactions of this group which have occurred within the last six years in the syphilis department, in the wards of the Johns Hopkins Hospital, and in private practice.

At the outset we wish to define our use of the term "dermatitis and allied reactions." The term is used to include all skin rashes, and certain reactions, such as stomatitis and itching, not characterized by any demonstrable skin lesion, induced by the chemotherapeutic arsenic preparations employed in the treatment of syphilis. All of these products, including arsphenamin, neoarsphenamin, sodium arsphenamin, silver salvarsan, and sulfoxylate salvarsan, have been observed to excite these toxic reactions.

Reactions of this group are generally stated in the literature to be rare. Fortunately, they are, but in this country, at least, where the common European encephalitis is almost unknown, they are the most frequent cause of death following the administration of arsphenamin; and when not fatal they are the most distressing and protracted of all arsenic reactions. Of ten deaths at the Johns Hopkins Hospital due to the arsphenamins, for example, two were cardiac (in patients with marked aortic and myocardial lesions), two were from causes unknown (probably impurity in the drug used), one was from acute yellow atrophy of the liver, and five were from reactions of the dermatitis group. Among the twenty-three patients which we report there were

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\* From the Syphilis Department of the Medical Clinic, Johns Hopkins Hospital.

four whose reactions place them in the "mild group" to be described, and eighteen in whom there were twenty-one instances of severe reactions, resulting in five deaths, a mortality of 27.7 per cent. Most of the remaining thirteen patients with severe reactions were seriously and uncomfortably ill, and the average hospital stay exceeded a month. The incidence of these reactions is well illustrated by the figures of Harrison<sup>1</sup> and of Parnell and Fildes.<sup>2</sup> The former found, in about 80,000 injections of arsphenamin products in 10,000 syphilitic patients, 124 cases of dermatitis, of which twenty-six were severe, twenty-four moderately severe, and seventy-four mild or fleeting. There were eight deaths. Parnell and Fildes noted thirty-eight cases of dermatitis in 1,250 men receiving 6,588 injections of neoarsphenamin. These figures indicate that one of every 645 injections of arsphenamin, and one of every 173 injections of neoarsphenamin, are likely to be followed

TABLE 1.—APPROXIMATE INCIDENCE OF REACTIONS BY YEARS

Year	Approximate Number of Doses of Arsphenamin Products *	Number of Reactions of Dermatitis Group
1914.....	3,000	2
1915.....	5,000	4
1916.....	6,000	2
1917.....	6,000	2
1918.....	7,000	—
1919.....	9,000	1
1920.....	11,000	10
Total...	47,000	21

\* From 1910 to 1915 the arsenical preparation in use was German salvarsan; early in 1915, the diarsenol brand of arsphenamin was substituted. Of the 47,000 injections noted in this table, at least 40,000 were of diarsenol; about 4,000 of salvarsan; 2,500 neoarsphenamin (novarsenobenzol Billon and Dermatological Research Laboratories). Any comparison of the number of reactions following the various brands should be viewed with a proper appreciation of the numbers of doses of each brand used.

by a reaction belonging to the dermatitis group. This is not quite in accord with our experience. One of us (Moore) was in charge of a syphilis clinic in France during the war. In the course of about 8,000 injections of novarsenobenzol (Billon), only nine cases of dermatitis were seen, none of them severe. In our experience in this country only two reactions of this group followed neoarsphenamin.

Table I shows the approximate incidence of reactions in the Johns Hopkins Hospital by years. Two of the twenty-three cases are excluded in this table because they resulted from arsenic administered elsewhere.

1. Harrison, L. W.: Critical Review; the Treatment of Syphilis, *Quart. J. Med.* **10**:291 (July) 1917.

2. Parnell, R. J. G., and Fildes, P.: A Clinical Study of the Toxic Reactions Which Follow the Intravenous Administration of 914, *Publ. Med. Research Com.*, London, 1919.

## ETIOLOGY

*Race and Sex.*—Table 2 shows the incidence of reactions by race and sex. No sex differences are apparent, but there is a striking preponderance of white patients when it is considered that the 9,000 (approximately) patients from whom this material is drawn are almost evenly divided between the white and colored races. One must conclude that such reactions are about three times as frequent in the white as in the colored race—an interesting etiologic observation.

*Lesions of Syphilis.*—As a hypothesis it might be conceived that syphilis may produce pathologic alterations predisposing to the production of toxic arsphenamin phenomena. For example, endothelial capillary damage in the early invasive stage of the disease might render these small vessels easily permeable and permit the transudation of arsenic into the skin in irritating quantities. That such endothelial injury does take place is well known. It is apparently the factor which leads to the macular syphilides and edemas which occur during the

TABLE 2.—INCIDENCE OF DERMATITIS AND ALLIED REACTIONS BY RACE AND SEX

Type of Reaction	White		Colored	
	Male	Female	Male	Female
Mild: urticarial, erythematous, herpetic....	—	4	—	—
Exfoliative group.....	8	5	2	1
Allied reactions.....	—	1	1	1
Total.....	8	10	3	2
	18		5	

earlier phases of the infection. Furthermore, late involvement of blood vessel walls, a not unusual feature of the disease, may interfere with an even distribution of the drug in the circulation, leading to toxic concentration in areas in which the vessel walls are intact; syphilitic interstitial hepatitis may to some extent inhibit the liver function of removing arsphenamin rapidly from the circulation, leading to long continued contact of the drug with the tissues in a concentration which then becomes toxic; foci of syphilitic inflammation may possess a positive affinity for the drug, which by overaction might lead to toxic concentration. One might speculate at length but we believe the evidence we have to offer will at once definitely dispose of such conceptions.

Of about 9,000 cases from which our material is drawn, in approximately 20 per cent., or 1,800 cases, the duration of syphilis was less than one year, and most of these patients were in the early primary or secondary stage. In the remaining 7,200 patients the infection was more than one year old; and the more deep seated visceral lesions may be assumed to have been established. The proportionate number of doses of arsphenamin given to each group was about the same, an

average of from seven to eight per patient. In Table 3 the milder rashes (urticaria, herpes, fleeting erythemas) have been excluded, because the exact number of cases of these types is unknown. On the other hand the numbers given for the macular, maculopapular, vesicular and exfoliative rashes and the allied reactions represent all cases of these groups which have occurred. It will be noted that in the 1,800 early cases, two such reactions occurred, or one in every 900 patients. Among the 7,200 late cases, there were fifteen reactions, an incidence of one to every 480 patients. If the probable statistical error is taken into account, considering the small number of cases of dermatitis, these figures do not show any especial tendency for reactions of this group to appear either early or late in the disease.

It is further worth noting that only one patient with early secondary syphilis showed evidence of gross vascular damage. It was noted in a preceding paragraph that reactions were three times as frequent in the

TABLE 3.—TYPE OF RASH IN EARLY AND LATE CASES OF SYPHILIS

Type of Rash	Early Syphilis		Late Syphilis (Duration More Than 1 Year)					Non syphilitic
	Primary	Secondary	Positive Wassermann	Cardio-vascular	Visceral	Tertiary Skin or Bone	C. N. S.	
Macular, maculopapular, mild vesicular.....	—	—	—	—	—	1	1	—
Exfoliative.....	—	1	1	—	—	3	1	2
Stomatitis, itching.....	1	—	—	—	—	—	—	—
Total by groups		2			15			2

white as in the colored race. Since late vascular syphilis occurs with somewhat greater frequency in colored patients, this ratio lends support to the view that such blood vessel alterations, at least, play no etiologic rôle. Furthermore, the fact that exfoliative dermatitis occurred in two patients clinically nonsyphilitic eliminates syphilis as a modifying influence upon the reaction.

*Drug implicated.*—No arsphenamin product which we have employed has been found to be free of these toxic effects. Five of the twenty-three patients developed reactions after salvarsan (German product); one after neoarsphenamin (Metz) (administered by an out of town physician); fifteen after the diarsenol brand of arsphenamin; two after the novarsenobenzol (Billon) brand of neoarsphenamin; and one after sodium cacodylate.

*Association with other drugs.*—In only five of our twenty-three cases was any other drug, in particular mercury or potassium iodid, used in conjunction with the arsenical product employed, or even at any time near the development of the reaction. This point is specifically

stated because of the difficulty in the differentiation of drug rashes, and the controversy which has raged in Germany over the possible identity of mercurial and arsenical dermatitis. It is, therefore, apparent that the arsenical preparation must be regarded as the only drug involved in the reaction.

*Dosage and number of doses.*—Table 4 shows the tendency of reactions of this group to appear early in the course of treatment, all but four occurring before the seventh injection. Contrary to the experience of most other observers, we have seen two reactions of this group occur after the first injection of the drug.

#### PREVIOUS REACTIONS

This part of the study is of much practical importance. It is essential to be able to recognize the prodromal symptoms of reactions of this group. In Table 5 the preparations used, the dosage, and the reaction

TABLE 4.—INCIDENCE OF REACTIONS OF DERMATITIS GROUP; NUMBER OF DOSES OF DRUG PRECEDING REACTION

Type of Rash	Reaction After Dose														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Mild: urticarial, herpetic, erythematous.....	1	—	2	—	—	1	—	—	—	—	—	—	—	—	—
Exfoliative group.....	2	3	2	1	3	2	1	—	—	—	—	1	—	1	—
Allied reactions.....	—	1	—	1	—	—	—	—	—	—	—	1	—	—	—
Total.....	3	4	4	2	3	3	1	—	—	—	—	1	1	1	—

following each dose are presented in tabular form. It will be noted that in six cases there were definite prodromal symptoms, appreciation of which should have led to caution in further treatment.

One patient (Case 6) who developed a mild maculopapular rash after each of two doses of diarsenol, also reacted to neoarsphenamin with herpes once, and after each of eight further doses, with marked malaise, usually lasting several days. The malaise seen in retrospect was out of all proportion to the size of the dose. After the ninth dose, the patient developed stomatitis and aplastic anemia and died.

In three patients (Cases 8, 11 and 19) a mild rash was disregarded and further arsenic administered. In one of these cases there was complaint of itching after the third and fourth doses of diarsenol, with a mild rash after the fifth; in spite of which a sixth dose was given. An unusually severe exfoliative dermatitis developed.

One of the patients (Case 12) reacted to four of six doses of diarsenol with unusually prolonged periods of fever. The seventh dose was followed by a fatal rash. The last patient (Case 10) developed a stomatitis which was regarded as Vincent's angina (on

insufficient evidence), and treatment persisted in, with the result that the stomatitis was markedly intensified and the patient made critically ill.

In the other sixteen cases there were no prodromata which seemed significant. However, we feel justified in calling attention to the danger of persistent arsenical therapy if there develops after any injection itching, a mild macular, maculopapular or vesicular skin rash, especially if there is any tendency to scaling, however slight, stomatitis, prolonged fever, or malaise out of proportion to the dosage administered.

*Dosage.*—Table 5 also indicates the dose of the drug administered. Generally speaking, there is apparent no tendency for skin reactions to occur more frequently after large than after small doses. For several years it has been our custom to give ambulant patients not more than 0.4 gm. arsphenamin or its arsenical equivalent of allied preparations; but no diminution in the incidence of reactions has resulted.

*Interval between treatments.*—Though not indicated in Table 5, the average interval between doses was one week. In most of the cases our routine plan of treatment was followed until interrupted by a reaction. This consists of courses of arsphenamin alternating with courses of mercury, the arsphenamin course consisting of six doses at weekly intervals, the mercury course lasting, depending on the stage of the disease and the amount of previous treatment, from six weeks to four months.

*Technic of administration.*—We are firmly of the opinion that the technic of administration of the arsphenamins has no effect in producing reactions of this group. In the syphilis clinic of the Johns Hopkins Hospital, and in the wards, ample provisions are made to guard against technical errors, and the technic has not varied in the six year period from which this material is drawn. The same may be said of the other drugs involved. There has been noted no tendency for these reactions to occur in groups on special days, when a break in technic might have occurred.

*Lot of drug employed.*—In only two instances has any relation appeared between the lot of drug employed and the incidence of these reactions. The second dose of salvarsan (0.45 gm.) given in Case 1 of Table 5 was half of a 0.9 gm. ampule, the other half of which was used in Case 2. This man did not develop a rash, but a week after the injection, and for three weeks thereafter, he complained of itching; and his blood showed characteristic changes in the leukocytic picture. Case 12 of Table 5 was one of five patients who each received 0.6 gm. from a 3 gm. ampule of diarsenol. Three of these patients had no reaction; the other developed jaundice and a blood picture showing



TABLE 5.—DRUG USED, DOSE AND REACTION AFTER EACH DOSE \*

Case	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7 or More	Remarks
1	S., 0.3 gm. None	S., 0.45 gm. See remarks	.....	.....	.....	.....	.....	Exfoliative rash 3 days after dose 2
2	S., 0.3 gm. None	S., 0.45 gm. See remarks	.....	.....	.....	.....	.....	Itching 1 week after dose 2
3	S., 0.6 gm. None	S., 0.6 gm. Mild vesicular rash	S., 0.6 gm. See remarks	.....	.....	.....	.....	Rash after dose 2 disregarded; fatal exfoliative rash 10 days after dose 3
4	S., 0.3 gm. None	S., 0.55 gm. See remarks	S., 0.3 gm. (5 mos. later) See remarks	.....	.....	.....	.....	Maculopapular rash 5 days after dose 2; 1 day after dose 3; hematuria
5	S., 0.5 gm. None	S., 0.5 gm. None	S., 0.6 gm. See remarks	.....	.....	.....	.....	Exfoliative rash 2 days after dose 3
6	D., 0.4 gm. Mild macular rash	D., 0.2 gm. Rash slightly intensified	N. A., 0.3 gm. (7 mos. later) Herpes simplex, severe malaise	8 injections N. A., all of 0.3 gm.; after each one, marked general malaise, chills, nausea, felt "knocked out," etc.; no further skin eruptions	.....	.....	.....	Fatal stomatitis and aplastic anemia 1 week after dose 11
7	N. A., 0.6 gm. Marked nausea and malaise	N. A., 0.6 gm. Same	N. A., 0.6 gm. Same	N. A., 0.6 gm. Same	N. A., 0.6 gm. See remarks	.....	.....	Exfoliative dermatitis 1 week after dose 5
8	N. A., 0.6 gm. None	N. A., 0.6 gm. None	N. A., 0.45 gm. Itching	N. A., 0.45 gm. See remarks	.....	.....	.....	Moderately severe exfoliative dermatitis 10 days after dose 4
9	D., 0.4 gm. None	D., 0.4 gm. None	D., 0.5 gm. None	D., 0.3 gm. None	D., 0.3 gm. Malaise	D., 0.2 gm. See remarks	.....	Moderately severe exfoliative dermatitis 7 days after dose 9
10	D., 0.3 gm. Chills, malaise	D., 0.2 gm. Malaise	D., 0.2 gm. Six days later, sore throat, headache	D., 0.3 gm. See remarks	.....	.....	.....	Progressively severe stomatitis after dose 4

11	D., 0.2 gm. Slight headache, chills	D., 0.3 gm. Nausea, head ache	D., 0.3 gm. Itching	D., 0.3 gm. Itching	D., 0.3 gm. Maculopapular rash 3 days later	D., 0.2 gm. See remarks	Severe exfoliative rash 2 days after dose 6
12	D., 0.2 gm. None	D., 0.3 gm. Temp. to 103 F., ringing from 100-101 F. for 3 days; malaise	D., 0.6 gm. None	D., 0.6 gm. Temp. to 101 F. for 1 day	D., 0.6 gm. Temp. to 102 F. for 1 day	D., 0.6 gm. See remarks	Fatal exfoliative rash, 1 day after dose 7
13	D., 0.3 gm. Nausea, vomit- ing, diarrhea, headache	D., 0.3 gm. None	D., 0.3 gm. None	D., 0.3 gm. None	D., 0.3 gm. See remarks	.....	Fatal exfoliative rash 1 day after dose 5
14	D., 0.4 gm. Nitritoid crisis See remarks	.....	.....	.....	.....	.....	Urticaria after dose 1
15	D., 0.3 gm. None	D., 0.3 gm. None	D., 0.3 gm. None	.....	.....	.....	Erythematous rash 4 days after dose 4
16	No reactions after any of 12 doses of diarsenol. Exfoliative dermatitis after dose 13						
17	D., 0.4 gm. See remarks	During the following year, 16 doses of neoarsphenamin without reaction; then sodium diarsenol 0.1 gm. See remarks					
18	D., 0.3 gm. None	D., 0.3 gm. Slight urticaria	D., 0.2 gm. Urticaria more severe	D., 0.1 gm. Severe urticaria	N. A., 0.6 gm. None	.....	Maculopapular rash after dose 1, repeated after dose 18
19	D., 0.3 gm. Chills, headache, malaise	D., 0.3 gm. Same	D., 0.3 gm. Same	D., 0.2 gm. Mild maculopapular rash 1 week later	D., 0.1 gm. (3 weeks later) See remarks	.....	Severe exfoliative der- matitis and jaundice after dose 5
20	D., 0.3 gm. None	D., 0.3 gm. See remarks	.....	.....	.....	.....	Exfoliative rash 4 day after dose 2
21	No noteworthy reactions after any of 17 doses of diarsenol. Exfoliative dermatitis after dose 18						
22	D., 0.2 gm. Fever	D., 0.3 gm. Drowsy	D., 0.3 gm. None	D., 0.3 gm. None	D., 0.3 gm. Nitritoid crisis	D., 0.2 gm. Profuse urticaria	.....

\*The drugs used are indicated by their initials; thus, S. is salvarsan, D., diarsenol, N. A., neoarsphenamin. For each patient there appears first the drug administered and the dose; below this reactions are briefly given.

a large mononuclear transitional increase. The record of this patient, however, is unfortunately too incomplete to include in the present series.

With the other patients, no such relation to the lot of drug can be traced. Twelve of the remaining twenty-one patients were treated in the Outpatient Department, and received their injections from the same lot of drug as about sixty other patients, none of whom developed similar reactions. This indicates that any apparent association of dermatitis reactions with the lot of drug used is only accidental, and that this factor plays no role in their incidence. This point is particularly emphasized since it practically rules out impurity in the drug as a causative factor.

#### CLASSIFICATION OF LESIONS

Our twenty-three patients have suffered from thirty-one reactions in this general group. These thirty-one reactions have been urticaria (six times) erythema (once), herpes simplex (twice), macular or maculopapular rashes (five times), exfoliative dermatitis (fourteen times), stomatitis (twice), and itching (once). The evidence has permitted us to classify these different manifestations into a mild and a severe group, on the basis of their constitutional manifestations and their significance as regards the further treatment of syphilis. In the mild group fall urticaria, erythema, and herpes; in the severe group the macular, maculopapular and exfoliative rashes, itching and stomatitis.

*Mild Rashes: Urticaria, herpes, erythema.*—Only those cases of urticaria so severe as to attract special notice have been included in this series. We have made no attempt to tabulate all such cases in our material, and are, therefore, unable to state with accuracy the incidence of this reaction. Urticaria has long been recognized as one of the immediate after effects of the injection of arsenical preparations. The wheals appear during the injection or within two hours afterward. Usually, the rash lasts only a few hours, in exceptional cases from several days to a week. It is common in association with nitritoid crises; and, having once occurred, is likely to occur again after repeated injection of the same drug. This rule is subject to variation. Urticaria may follow several injections, then disappear, not to occur again; or it may occur infrequently throughout a whole course of treatment.

We have observed no accompanying constitutional manifestations, except those associated with the nitritoid crisis. The temperature is normal, and studies of the urine and blood fail to reveal any abnormalities. In view of the importance we attach to changes in the blood picture in the severe types of reactions, this point has been specially investigated in patients with urticaria, with negative results.

In our experience, the occurrence of urticaria has no significant bearing on further arsphenamin therapy. In most instances it may be disregarded, and more arsphenamin administered with the certainty that sooner or later the tendency to hypersensitiveness will be lost. It is an interesting fact that a patient who develops urticaria after one drug will often fail to develop it if a different preparation is used. Thus one patient (Case 18 of Table 5) had very severe attacks of urticaria after the second and third dose of diarsenol (0.3 gm. each), but did not develop it at all after five subsequent doses of neoarsphenamin. The prognosis is uniformly good. As stated above, no grave constitutional disturbances have been observed, and no patient has been seen who, after having had urticaria, later developed a more serious dermatitis.

We have not noted, as has been mentioned by Emery and Morin<sup>3</sup> and by Saphier,<sup>4</sup> late cases of urticaria coming on several days after the injection and simulating serum disease by its association with fever and joint pains.

The treatment of these reactions is that of urticaria in general. The eruption can be controlled completely by the repeated use of epinephrin intramuscularly, which may also be used as a prophylactic, given before the injection of arsphenamin.

*Herpes simplex* may be attributed directly to the action of arsenical preparations. It may be severe, as in one patient in whom the chin, lips, tongue and buccal surfaces were literally covered with large herpetic lesions. It is rare, only two cases having been noted; and it is apparently of no significance as a contraindication to further treatment, since continuation of arsenic therapy (of both the same and different drugs) has been without ill effect in both these patients. We have seen no cases of herpes zoster.

A fleeting erythematous rash has also been seen in several patients. The rash is usually a diffuse dusky red erythema, blanching readily on pressure, and involving the buccal mucosa as well as the skin. It may be accompanied by a moderate elevation of temperature. Usually it fades rapidly and has completely disappeared within three days. Further injections of the same and different drugs have been unaccompanied by any reaction.

In both these groups, aside from a mild fever, accompanied often by leukocytosis, no constitutional disturbances have been observed. Studies of the urine, kidney function, and blood have all been negative.

3. Emery and Morin: Accidents des arsénobenzènes et anaphylaxie. Paris méd. 35:80, 1920.

4. Saphier, J.: Ein Fall von Salvarsan—Allergie, München. med. Wehnschr. 46:130, 1919.

*Macular, Vesicular and Exfoliative Rashes.*—The more important group includes the macular and maculopapular rashes, vesicular eruptions, exfoliative dermatitis, and certain allied reactions. We regard the skin manifestations of this group as degrees of the same process. We have occasionally seen a mild macular rash assume vesicular or exfoliative characteristics.

The time of appearance of rashes of this type varies from twenty-four hours to fourteen days. In thirteen cases in which the interval between the last dose and the appearance of the rash could be determined with certainty, the average was 4.6 days. The wide variation in individual cases is doubtless due to the fact that it is impossible to determine the exact effect of any given dose in the production of the rash.

The characteristics of the rash have been described so often that a too detailed account is superfluous. It begins as a maculopapular or vesicular dermatitis, often limited to the extensor surfaces of the limbs, but rapidly spreading until the whole body (scalp, face, trunk, extremities, palms and soles) is involved. In the milder cases, particularly of the macular or maculopapular type, the process may stop with this, and the eruption disappear in a few days. Frequently, there is a late fine branny exfoliation. In the more severe maculopapular, and especially the vesicular eruptions, marked scaling and exfoliation usually takes place, and the skin of the entire body is desquamated in large flakes. Often an entire palmar or plantar surface comes away intact. The rash is accompanied by the most intense and distressing itching. Usually, the exfoliation is complete in from three to four weeks, but in some cases healing may take much longer. Once or twice it has been noted that several distinct exacerbations have occurred in the same patient, the skin continuing to exfoliate periodically for several months.

The exfoliative process is in some cases so extensive as to produce minor complications, such as severe conjunctivitis, due to the complete desquamation of the conjunctival epithelium; temporary deafness, from heaping up of the exfoliated epithelial debris in the external auditory canal; and, in women, vaginitis. Diarrhea is not uncommon, and the stools may for a short time contain large amount of mucus and epithelial cells. The buccal surfaces may also be involved, the tongue and cheeks being thick and swollen, and the epithelial covering desquamated.

The graver complications which may occur with exfoliative dermatitis are: arsenical neuritis, jaundice, skin infection, bronchopneumonia and acute nephritis.

Peripheral polyneuritis was uncommon in our series, being noted in only two patients. It consists of pain, abolition of deep reflexes, espe-

cially in the legs, and sensory disturbances. Beeson<sup>5</sup> describes a case of exfoliative dermatitis complicated by polyneuritis, and reviews this phase of the literature.

Jaundice has also been noted by several authors. It has been ascribed directly to liver damage, generally of the type of acute yellow atrophy. It occurred in three of the eighteen patients in our series. In each case, however, it was mild, a late phenomenon, and was apparently of no significance.

Skin infection played an important rôle in the prolongation of the illness of nine cases, and was a contributory factor in the death of two. It is due to the universal weeping eczematous character which the eruption ultimately assumes. Cracks and fissures in the skin are large and numerous, scratching is almost impossible to prevent and the inevitable entrance of the common skin organisms produces painful and, at times, serious furuncles and carbuncles. Two of our patients died of streptococcus septicemia following extensive skin infection.

Since, as we have seen above, exfoliation is not confined to the skin, but may also involve the epithelial lining of such structures as the conjunctiva, buccal surfaces, external ear, vagina and gastrointestinal tract, it is not unusual to note also a denudation of the mucous membrane of the trachea and bronchial tree. Thus, bronchitis is frequent, and if the process has been sufficiently extensive, bronchopneumonia follows as a logical sequence. This has occurred in four of our patients. The pneumonic consolidation is often extensive. Both the bronchopneumonia and the skin infection are furthered by the lack of bodily defense against bacterial invasion, which, in turn, is caused by the direct action of the arsenic on the bone marrow, as shown by the blood picture.

Studies of the urine and of renal function in these cases are of interest. In about 80 per cent. of the patients there is evidence of more or less severe damage to the kidneys. Albumin usually appears in amounts varying from a trace to 3 gm. per liter; casts are present; and in several cases, notably those with skin purpuric manifestations, microscopic and chemical blood has been found. In two of the fatal cases there has been noted a rapid decrease in the phenolsulphonephthalein output to practically nothing; and in these patients the urea nitrogen and nonprotein nitrogen of the blood has risen rapidly. Not all of the severe or fatal cases have shown this phenomenon, however; in a few the kidney function remained apparently unimpaired. A few of the patients have given evidence that the acute nephritis has been transformed into a chronic nephropathy, and that some residual kidney damage is permanent.

5. Beeson, B. B.: Polyneuritis Plus Dermatitis Exfoliativa Following Neo-Arsphenamin, *Arch. Dermat. & Syph.* 2:337 (Sept.) 1920.

Thirteen of eighteen patients had, throughout the course of the rash, a rise in temperature ranging from 100 to 105 F. usually lasting from two to four weeks. Two cases were afebrile, and in three no observations were made. The temperature curve is usually irregular and remittent; in some cases a definite infectious agent can be found to explain it in the complications discussed above—skin infection and bronchopneumonia; in others no cause is demonstrable.

Four patients developed at one time or another during the rash, many petechial hemorrhages throughout the skin. These were among the more serious cases; and of these four patients, two died.

In the course of routine study of cases of this type, our attention was directed to changes in the blood picture which have generally been unrecorded. Previous reports<sup>6</sup> from the Johns Hopkins Hospital have called attention to this phenomenon. Eleven of our eighteen patients with exfoliative and maculopapular rashes have been studied carefully from this viewpoint, and the results are summed up in Table 6.

It will be seen that there is practically no evidence of damage to the erythropoietic function of the bone marrow, except in one severe fatal case, in which a typical aplastic anemia occurred. There is usually leukopenia, which may be marked (600 W. B. C. per cu. mm.), but which may be modified by the presence of intercurrent infection to produce a leukocytosis. In the differential picture the outstanding features are marked alteration of all the leukoblastic cells of the bone marrow, the lymphoid elements remaining largely unharmed. There is an absolute and relative decrease in the polymorphonuclear neutrophile cells (which may even completely disappear). The basophile cells if affected at all are slightly increased. Eosinophilia, which may reach unusual proportions (56 per cent.), was noted in 10 cases. It persists over long periods of time, in one case more than three months. There is frequently a marked increase in the other cells of bone marrow origin, the large mononuclear-transitional group, which may also reach unusual heights (50 per cent.) (Table 7). Usually, when there is a great increase in this cell group, eosinophilia is either absent or slight, and vice versa; though occasionally (Case 7 of Table 6) both groups may be increased.

Many of the leukocytic cells in the circulating blood are abnormally fragile, and apparently break down into unrecognizable smudges. Occasionally, a few myelocytes, myeloblasts, or so called "irritation forms"

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6. Evans, F. A.: Observations on the Origin and Status of the So-Called Transitional White Blood Cell, *Arch. Int. Med.* **17**:1 (Jan.) 1916. Moore, J. E., and Foley, F. E. B.: Serious Reactions from the Salvarsan and Diarsenol Brands of Arsphenamin: Unusual Blood Pictures, with the Report of a Fatal Case, *Arch. Dermat. & Syph.* **1**:25 (Jan.) 1920. Moore, J. E., and Keidel, A.: Stomatitis and Aplastic Anemia Due to Neo-Arsphenamin (to be published).

Case	Drug	Type of Rash	Severity of Rash	Alterations in Red Blood Cells	Alterations in Hb. Content	Alterations in Total Leukocytes	Polymorpho-nuclears	Complete Differential Picture at Height of Reaction					Abnormal Cells	Remarks
								Baso-phils	Eosino-phils	Small Mononuclears	Large Mononuclears; Transitionals			
1	Salvarsan	Exfoliative	Severe	None	None	At first no change; later leukocytosis (see remarks)	Early marked decrease (7.2%)	.....	Late eosinophilia (6.47%)	Relative decrease	Marked increase (64.8%) lasting 5 weeks	A few myelo-cytes	Pericarditis at time of leuko-cytosis; pur-puric skin le-sions	
2	Salvarsan	Exfoliative	Mild	9 normo-blasts in 300 cells	?	?	Decrease (47%)	.....	Eosinophilia (24.6%)	.....	No noteworthy change	.....	Uncomplicated	
3	Sodium cacodylate	Exfoliative	Severe, fatal	None	None	None	?	.....	Eosinophilia (38%)	.....	.....	.....	Nonsyphilitic; Hodgkin's disease	
4	Novarsopneummin (Metz)	Exfoliative	Severe	None	None	Leukocytosis	Relative and absolute decrease (44.7%)	.....	Eosinophilia (37%) lasting 2 weeks	.....	No noteworthy change	A few fragile cells and myelocytes	Severe skin infection accounts for leukocytosis	
5	Novarsenobenzol (Bilom)	Exfoliative	Moderately severe	None	None	At first no change; later slight leukopenia (4,000)	Slight decrease (68%)	.....	Slight eosinophilia (4 to 5%)	.....	Moderate and relative increase (17.5%)	Many fragile cells	Uncomplicated	
6	Diarsenol	Exfoliative	Mild	None	None	None	Relative and absolute decrease (54%)	.....	Eosinophilia (11.5%) lasting 1 month	.....	Slight increase (12.5%)	Many fragile cells	Uncomplicated	
7	Diarsenol	Exfoliative	Severe	None	None	Leukopenia (3,840)	Marked relative and absolute decrease (10.6%)	Slight persistent basophilia (3%)	Eosinophilia (28%) lasting 4 weeks	.....	Marked relative and absolute increase (44%) lasting 4 weeks	Numerous atypical large mononuclear cells	Uncomplicated	
8	Diarsenol	Exfoliative	Severe, fatal	Marked secondary anemia; no evidence of regeneration	Increasing leukopenia; white blood cells 100 before death	Increasing leukopenia; leukocytosis (see remarks)	Final complete disappearance of polymorpho-nuclears	.....	Absent	Practically only remaining cells	Almost complete disappearance	.....	Uncomplicated; purpuric skin lesions	
9	Diarsenol	Exfoliative	Severe, fatal	Secondary anemia	Leukopenia followed by leukocytosis (see remarks)	Leukopenia followed by leukocytosis (see remarks)	Slight decrease (47%)	.....	Late eosinophilia (5.37%)	.....	Early increase (11%) followed by almost complete disappearance at height of eosinophilia	.....	Skin infection accounts for late leukocytosis; purpuric skin lesions	
10	Diarsenol	Exfoliative	Moderately severe	None	None	Leukopenia (2,800)	Marked decrease (25%)	Slight late increase (5%)	Normal	.....	Very marked increase (56%) lasting more than 3 weeks	.....	Uncomplicated	
11	Diarsenol	Exfoliative	Moderately severe	None	None	Leukopenia (4,200)	Marked decrease (38%)	.....	Eosinophilia (10%)	.....	No change	Many fragile cells	Uncomplicated	
Summary.....							In 10 cases marked absolute and relative decrease	In 2 cases slight basophilic	In 9 cases marked persistent eosinophilia	Usually no absolute change	In 6 cases slight or marked increase; 3 times no change; once (severe case) considerable decrease	In 5 cases many fragile cells; in 1 case about normal cell forms (myelocytes, myeloblasts, reticulation forms)		



may appear, indicating some effort at regeneration on the part of the leukopoietic centers of the marrow. Unfortunately, the platelets have not been counted, though in some cases (especially those with purpuric manifestations) they have seemed in the stained smear to be decreased.

For detailed accounts of the blood findings in five cases of this type, the reader is directed to earlier articles. For the sake of completeness, the studies of the blood of two cases, with brief abstracts of the histories, are presented in Table 7.

TABLE 7.—COMPLETE BLOOD STUDY IN TWO CASES

Date	Red Blood Cells	Hb., per Cent.	White Blood Cells	Differential Count (per Cent.)					Remarks
				Polymorphonuclears	Basophils	Eosinophils	Small Mononuclears	Large Mononuclears; Transitional	
Case 1 *									
2/ 9/20	4,216,000	70	7,960	47.0	0.66	6.0	33.3	13.0	Four days after onset of reaction
2/11/20	.....	..	6,600	63.6	0.0	10.3	23.3	3.0	
2/12/20	.....	..	8,080	51.0	0.0	10.0	35.0	4.0	
2/13/20	.....	..	9,320	56.0	0.3	15.6	22.3	5.6	Skin infection and bronchopneumonia accounts for leukocytosis
2/17/20	5,584,000	75	17,240	67.3	0.0	23.3	6.0	1.3	
2/19/20	.....	..	.....	68.5	1.3	15.0	14.6	3.6	
2/25/20	3,736,000	88	23,900	85.0	0.0	3.6	11.0	0.3	Patient died
2/27/20	.....	..	.....	.....	.....	.....	.....	.....	
Case 2 †									
11/ 3	6,000,000	85	4,800	49.0	.....	2.0	19.0	30.0	Platelets, 132,000
11/ 4	.....	..	3,200	25.0	1.0	.....	24.0	50.0	
11/ 5	.....	..	3,400	35.5	.....	1.0	16.0	48.5	
11/ 6	6,464,000	83	3,000	38.0	.....	1.0	16.0	45.0	
11/ 7	.....	..	2,800	36.0	2.0	3.0	23.0	36.0	
11/ 8	.....	..	3,600	33.0	.....	2.0	28.0	37.0	
11/ 9	.....	..	3,000	39.0	3.0	2.0	26.0	29.0	
11/10	.....	..	3,000	34.0	5.0	1.0	19.0	41.0	
11/11	.....	..	3,800	42.5	2.0	2.0	23.5	30.0	
11/12	5,960,000	80	4,600	57.5	1.0	0.5	20.5	20.5	
11/13	.....	..	4,500	.....	.....	.....	.....	.....	
11/14	.....	..	4,600	39.0	0.5	2.0	23.5	35.0	
11/15	.....	..	4,000	34.5	.....	1.5	29.5	34.5	

\* Patient, a white woman, aged 31, was treated for a gumma of the soft palate. Five doses of diarsenol, 0.3 gm. each, were given at weekly intervals, the last dose February 4. The next day appeared a profuse macular rash, rapidly becoming vesicular and exfoliating. About February 15, there developed an intractable diarrhea, extreme generalized edema, skin infection and bronchopneumonia. The patient died twenty-two days after the onset of the reaction. Necropsy was not permitted.

† This patient was a white woman, aged 38, nonsyphilitic, with a sarcoma of the choroid. As a therapeutic test was requested by the ophthalmologist, she was given two doses of diarsenol, 0.3 gm. each, October 21 and 28. Four days later she developed a typical exfoliative dermatitis which ran the usual course, uncomplicated by skin infection or bronchopneumonia.

That the eosinophilia is not to be ascribed to the skin lesion is evident from the study of the blood in patients suffering from stomatitis and itching, in whom the blood changes constitute the reason for classifying such reactions as allied to dermatitis.

One of the striking features of the rashes of this group is their tendency to recurrence after further arsenical therapy. This has been

emphasized in the past, so that in the minds of many syphilologists the occurrence of a rash of any type is a sufficient signal for the discontinuance of all further arsenic therapy. It has been pointed out that for the urticarial, herpetic and erythematous rashes, this does not hold good. In rashes of the maculopapular and exfoliative type, it is a factor of great importance; as may be seen from the following case:

M. A., a white woman, aged 37, had in April, 1916, a very severe exfoliative dermatitis after the sixth of a series of doses of diarsenol of 0.3 gm. each, except the last, which was 0.2 gm. She was desperately ill for a time, and was in the hospital four weeks. In November, 1917, eighteen months later, she was given 0.1 gm. diarsenol, and within three days developed another exfoliative rash of almost as great intensity as the first.

The second reaction may differ in type from the first as in the case of one patient (J. H.) who developed a moderately severe maculopapular rash after the third dose of arsphenamin. Five months later, another injection of the same drug was given, which did not cause a rash. On the following day, however, blood was found in the urine chemically and microscopically. No further treatment was given. How long this intolerance to the drug persists we do not know, since we have thought it wise to avoid clinical experimentation.

An observation of importance to the patient, however, has been made in this connection in the course of our study. If exfoliative dermatitis or an allied reaction is noted after the use of one arsenic preparation, a similar intolerance does not appear to exist in most cases for other drugs. Thus it is not always necessary completely to abandon arsenic treatment in a patient who may be badly in need of it. In six cases of exfoliative and maculopapular dermatitis, a change in the arsenic preparation has been attempted, with satisfactory results in four. An illustrative history follows:

R. L., white male, aged 38, with a gumma of the nasal septum, showed a generalized maculopapular rash twenty-four hours after the first dose of diarsenol, 0.3 gm. This itched intensely, did not exfoliate, and disappeared in about ten days. For fear of transforming this comparatively mild reaction into a grave one, diarsenol was discontinued, but two weeks after the first injection, 0.3 gm. neo-arsphenamin was administered. This was followed by no reaction. During the next year, nineteen doses of neo-arsphenamin, ranging from 0.6 to 0.9 gm., were given, none followed by any reaction whatever. One year from the date of the first dose of diarsenol, an injection of 0.1 gm. sodium diarsenol was given to determine if the original intolerance had been lost. This was followed by a severe general reaction (chills, fever, malaise, nausea) and the rapid appearance of a sparse maculopapular rash, which lasted four days. Again, further injections of neo-arsphenamin were without ill effect.

As opposed to cases of this sort we may mention an example in which the outcome was less happy.

L. H., white woman, aged 50, with primary syphilis, showed early signs of intolerance to diarsenol. Two days after the first injection of 0.4 gm. she developed a mild maculopapular rash, which was considerably intensified after the second dose of 0.2 gm. Arsenic treatment was discontinued and was not resumed for seven months, at which time 0.3 gm. neo-arsphenamin was given. This was followed in two days by a profuse outbreak of labial herpes, but no generalized rash. Succeeding doses of neo-arsphenamin, eight in all, led to the occurrence of no rash; but we should, perhaps, have been warned by the intense general malaise and "knocked out" feeling which followed each injection. One week after the last dose she developed stomatitis, an intense aplastic anemia, together with the characteristic leukocytic reaction described above, and after an illness of a month, she died.

These cases lead one to the conclusion that in some instances of this group, which unfortunately cannot be designated accurately beforehand, further arsenic therapy is possible, provided another drug is substituted for the one which originally produced the reaction. However, such a substitution should be begun very cautiously. If arsphenamin is to be substituted, the first dose should not be more than 0.005 gm.; if neoarsphenamin is used, not more than 0.01 gm.; and increase in dosage should be undertaken with caution. After each injection, the patient should be under careful observation, and the occurrence of any of the symptoms previously mentioned as prodromata should be the signal for abandonment of arsenic therapy. The interval between injections should be prolonged to at least two weeks instead of one week, in order to allow plenty of time for the development of untoward symptoms; and these precautions should be continued until the tolerance to the new drug is established.

Furthermore, studies of the blood should be carried out during such an attempt. This paper and the others of this series have shown that characteristic changes in the blood are an essential part of the reaction, and that such changes may occur in the absence of any evident skin lesions. It may be accepted as a fact that leukopenia, a marked decrease in the number of neutrophil cells, eosinophilia, increase in the large mononuclear-transitional group, or the appearance of many fragile or abnormal forms are of serious portent.

Another method of the possible determination of loss of intolerance to arsenic preparations has recently been suggested by Stuart and Maynard,<sup>7</sup> who propose an intradermal skin reaction. They found that such injections of minute quantities of arsphenamin produced a positive skin reaction in two of three cases of exfoliative dermatitis,

7. Stuart, H. C., and Maynard, E. P.: Hypersensitiveness to Arsphenamin Following Exfoliative Dermatitis: A Cutaneous Test, *Arch. Int. Med.* **26**:511 (Nov.) 1920.

some months after the reaction. We have attempted the use of a similar test, but we used the method of scarification, which Stuart and Maynard warn against. Only negative results have been obtained.

The prognosis of reactions of the exfoliative dermatitis group is grave. Among our cases there have been four deaths (with an additional one among the allied reactions to be described, a mortality of 27.7 per cent. The deaths occurred once after the salvarsan brand of arsphenamin, once after sodium cacodylate (administered elsewhere), and twice after diarsenol. In two instances, death was due to septicemia, the portal of entry in all probability having been through the damaged skin. A third death was apparently due to the accompanying aplastic anemia.

In general, the necropsy findings were the same in the three cases studied. There were innumerable hemorrhages throughout all the organs, more intense in the lungs, gastro-intestinal tract and kidneys. The hemorrhagic nephritis in one case was extreme. The bone marrow, in two cases examined, was markedly aplastic, with, as the outstanding feature, an almost complete absence of orderly leukopoietic centers. In two cases there were noted, especially in the lungs, areas of bacterial invasion without the usual cellular exudate. As previously pointed out, Winternitz and Hirschfelder<sup>8</sup> found a similar non-cellular exudate in the pneumonia of experimental animals whose bone marrow had been destroyed.

The treatment of reactions of this type is almost wholly a question of nursing. For the alleviation of the itching calamine lotion may be used. It has been found that the prevention of skin infection, with its resultant possible general septicemia, can sometimes be accomplished by frequent changes of sterile night dress and sheets. Sterile surgical stockings for the legs are also an aid. The hands may have to be bandaged to prevent scratching. If skin infection does occur, continuous baths of 1:50,000 mercuric chlorid solution may prove helpful.

The general therapy resolves itself into an attempt at elimination by saline purgatives and diuresis. Diaphoresis should not be employed because of the already damaged skin. For the severer forms of aplastic anemia occasionally seen, repeated transfusions of matched blood have been tried, but so far as we have been able to see, without beneficial effect.

#### ALLIED REACTIONS

Under this head we include itching without a skin rash (which we regard as a prodrome of dermatitis), and stomatitis.

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8. Winternitz, M., and Hirschfelder, A. D.: *J. Exper. M.* **17**:657, 1913.

That the symptom of itching is not one lightly to be disregarded is shown by the fact that if arsenic therapy is persisted in, a severe exfoliative dermatitis may develop (Case II, Table 5). It may also be associated with marked constitutional changes, as in Case 2, Table 5 (previously reported in detail), in which characteristic changes in the blood picture were noted. After the second dose of salvarsan, the patient showed, during his period of itching, a marked relative and absolute decrease in the polymorphonuclear neutrophils (34 per cent.), eosinophilia (12 per cent.) and a large mononuclear-transitional increase (23.5 per cent.), with the appearance of a few myelocytes.

Two cases of stomatitis are included in this group, both of which have been made the subjects of separate reports.<sup>9</sup> In both these cases, there was no dermatitis whatever, and neither patient had taken mercury (the first never, the second not for seven weeks before the onset of the reaction). The stomatitis was very severe, involving not only the gums, lips and cheeks, but the posterior pharynx as well. In one case, Vincent's organisms were demonstrated, but are to be regarded as secondary invaders. The clinical characteristics of the stomatitis almost exactly simulate those following the incautious use of mercury.

In each case the blood picture forms the basis for its inclusion in this group. In the first case there was leukopenia (2,800 leukocytes) with a complete absence of polymorphonuclear neutrophils, no eosinophilia, and a marked increase in the large mononuclear-transitional group (39 per cent.). Three weeks after the onset of the reaction, there was a normoblastic crisis, immediately preceded by a fall by crisis in the temperature from 103 F., and thereafter rapid recovery.

In the second case, there was a rapidly progressing fatal aplastic anemia, together with extreme leukopenia (600 leukocytes), almost complete disappearance of neutrophils and of the other leukocytic groups of bone marrow origin, and a complete absence of attempts at regeneration. In both cases there was hematuria, and in the second case, typical severe purpura. It will at once be noted that these changes in the blood are in all respects similar to those observed in the more severe cases of exfoliative dermatitis.

The condition of the mouth, therefore, should be kept under close surveillance during all antisyphilitic treatment. The occurrence of stomatitis should lead to a general survey of the patient, especially to blood studies; and changes in the blood, such as we have described, should lead to the suspension of arsenic therapy, which should be resumed only after an interval of several months and with due caution.

## DISCUSSION

The literature regarding these reactions, which is voluminous, consists in great part of case reports.<sup>9</sup> We have not attempted, therefore, to review every article in detail, but have limited the scope of our discussion to the five points raised by our own material: (1) the classification of reactions of this group; (2) the inclusion of stomatitis as a member of the group; (3) the significance of the changes in the blood; (4) the practical importance of the possibility of substitution of another arsenic preparation for the one causing the reaction, and (5) the etiology of such reactions, in particular those of the graver type.

A first consideration in the classification of dermatitis is the proper evaluation of the causative influence of arsenic. Drug rashes, especially exfoliative dermatitis, due to mercury were not unknown before the introduction of the arsphenamins, and there has been disagreement, especially in Germany,<sup>10</sup> over the rôle played by arsenic in these phenomena. Bine's<sup>11</sup> case illustrates the difficulty of deciding whether a toxic rash is due to arsenic or mercury, when both drugs are given together. Since the majority of our patients received no drug except arsenic, there can be no confusion on this point.

Harrison<sup>1</sup> classifies his 128 cases of dermatitis as severe, moderately severe and mild, the two former groups including all the cases of dermatitis in which exfoliation was noted, and the latter all instances of limited urticaria. He does not attempt an interpretation of this grouping, and states that "treatment was stopped, or continued very cautiously, after the slightest sign of skin trouble."

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9. Didry: *Dermatite exfoliative généralisée consécutive à des injections de* 606, *Ann. de mal. ven.* **11**:723, 1916.

Frühwald, R.: *Ueber Medikamentöse Spätexantheme nach Intravenöse salvarsan injektionen*, München. med. Wchnschr. **58**:2109, 1911.

Glombitza: *Spät-exantheme nach Salvarsan natrium injektionen, zugleich ein Beitrag zur viscerale Frühluës*, Deutsch. med. Wchnschr. **43**:1452, 1917.

Malherbe, H.: *Accidents cutanées dûs à l'emploi du 606*, *Ann. de mal. ven.* **12**:662, 1917.

Nussbaum, O.: *Erythema scarlatiniforme nach Salvarsan intoxication*, Deutsch. med. Wchnschr. **44**:468, 1918.

Leonard, L. G.: *Severe Dermatitis During Treatment with Novarsenobillon*, *Brit. M. J.* **2**:773 (Dec. 13) 1919.

Lau: *Dermatitis Exfoliativa Following the Administration of Salvarsan*, *J. Cutan. Dis. & Syph.* **37**:403, 1919.

Ffrench, E. G.: *Exfoliative Dermatitis Occurring During Treatment with Arsenic*, *Lancet* **1**:1262 (June 12) 1920.

10. Wechselmann: *Ueber die Verwechslung von Quecksilber und Salvarsan exanthema*, München. med. Wchnschr. **48**:1638, 1915.

Brandweiner: *Quecksilber oder Salvarsan dermatitis*, *Wien. klin. Wchnschr.* **29**:290, 1916.

11. Bine, R.: *Exfoliative Dermatitis Following Neo-Salvarsan Injections*, *Boston M. & S. J.* **175**:96, 1916.

Parnell and Fildes<sup>2</sup> divide their material on the basis of the skin manifestations. Of the thirty-eight rashes, twelve were erythematous, fourteen macular, four papular, two follicular, one polymorphic and nine unclassified. In two cases jaundice co-existed. Except in one patient, all the rashes were relatively mild, and in general, further arsenical therapy was possible.

Brauer<sup>12</sup> recognizes that the significance and etiology of the various dermatoses is not the same, and adopts a classification which closely approximates our own. He divides all arsphenamin dermatoses into two groups, primary and secondary. In the primary group he includes the "genuine toxic exanthems," and the skin lesions produced by the local infiltration of the drug into the tissues, necrosis and gangrene. He saw sixteen instances of such general toxic rashes in thirteen of 1,500 patients. Of these nine were erythematous, scarlatiniform or morbilliform, with or without stomatitis; one was erythematous-urticarial, complicated by edema; two were exudative erythema multiforme; one was purpura rheumatica with erythema nodosum; and one was severe universal pemphigoid dermatitis. To seven of these patients more salvarsan was administered after the eruption had subsided, and in only three cases was there recurrence of a rash. Brauer states that it is impossible to predict the likelihood of recurrence in any given case.

As secondary dermatoses he includes herpes simplex and zoster, hyperidrosis, alopecia, alterations in the nails, jaundice, melanoses occurring after primary rashes and immediate macular and urticarial rashes. He considers the etiology of this group to be other than the actual toxic effect of arsenic. For example, he suggests that urticarial rashes are to be regarded as a Herxheimer reaction, and are due to the destruction of foci of spirochetes in the skin.

We are in complete agreement with the general aspect of this classification, except that we feel that some of the cases which Brauer regards as primary, especially mild erythematous and morbilliform eruptions, should certainly belong to his secondary group.

Milian<sup>13</sup> has recently drawn attention to the obscurity in the classification of arsenical dermatoses. He divides them into two main groups, on the basis of etiology. The only skin manifestation which he regards as directly due to arsenic is exfoliative dermatitis, which in its early stages may be scarlatiniform, maculopapular, or vesicular. He notes particularly the association of edema with such cases. All other dermatoses he believes are of infectious origin: that is, they are acute

12. Brauer, A.: Zur Kenntnis der Salvarsan Dermatosen, *Dermat. Ztschr.* **19**:800, 1912.

13. Milian, G.: L'érythème arsenical oedémateux desquamatif, *Bull. et mém. Soc. méd. d. hôp. de Paris* **43**:1055, 1919.

exanthemata, such as measles or rubella; or they are due to the lighting up of latent bacterial infection following the temporary general lowering of resistance after intravenous arsphenamin therapy.

Our experience leads us to believe that as to the herpetic and erythematous rashes this latter conception may be true; but we do not feel that any of the eruptions we have seen were measles, rubella, or other acute exanthems. Furthermore, we are unconvinced by the cases<sup>14</sup> which Milian cites in support of this contention.

Recently several German authors have described arsenic exanthems unlike any we have observed. So far as we know, no similar cases have been reported in the American literature. Fuchs<sup>15</sup> relates the case of a woman with florid secondary syphilis, whose treatment consisted of five courses of combined arsphenamin and mercury. During the fifth course, the patient stated that since the beginning of this course, she had noted, after each injection, a brown spot on her leg which itched intolerably. Examination revealed a sharply circumscribed brown spot on the inner side of the left thigh about the size of a German mark piece. The skin was elsewhere unaltered. Ninety minutes after the injection of 0.45 gm. neoarsphenamin this spot was markedly reddened, its edges flaming red, and there was much itching and burning. One hour later the irritation began to subside, and within two hours the area looked as it had before the injection. Eight days later the spot was painted with a concentrated solution of neoarsphenamin, and the same phenomenon occurred. On the same day the patient was given 0.45 gm. sodium salvarsan. The local reaction was observed to be much less than after neoarsphenamin.

In another patient with neurosyphilis, it was noted in 1915 that after each injection of 0.45 gm. neoarsphenamin there was a marked reddening of the right bulbar conjunctiva. During 1916 and 1917 sodium salvarsan was used and the reaction did not occur. In 1917, one dose of neoarsphenamin caused the conjunctival reddening to re-appear. In 1919, when an injection of 0.45 gm. neoarsphenamin was preceded by 0.5 cm. epinephrin, the reaction was delayed and weaker; and on later attempts epinephrin suppressed it altogether.

Similar cases, to which the name of "fixed" salvarsan exanthem has been given, have been described by Schonfeld,<sup>16</sup> Naegeli,<sup>17</sup> and others. Naegeli's cases are similar to those cited, except that in one

14. Milian, G.: *Arsénobenzol erythèmes et rubéola*, Paris méd. **35**:131, 1917.

15. Fuchs, D.: *Fixe Salvarsanexantheme*, Deutsch. med. Wchnschr. **45**: 1276, 1919.

16. Schonfeld, W.: *Fixe Salvarsan exantheme*, Deutsch. med. Wchnschr. **46**:11, 1920.

17. Naegeli, O.: *Fixes Neosalvarsan exanthem und Adrenalinwirkung*. Cor.-Bl. f. schweiz. Aerzte **39**: 1917. Cited by Fuchs.



the reaction occurred in a naevus, and in the other in a conjunctiva damaged by disease. Because of this he suggests that the marked vascularization might explain the basis of the sensitization. The cases of the other authors cited do not lend support to this view. A case reported by Leibkind<sup>18</sup> is similar, except that the recurrent exanthem, which was more generally distributed, usually lasted several days rather than a few hours.

*Stomatitis as a reaction allied to dermatitis.*—Stomatitis due to the arsenicals has, so far as we have been able to discover, received practically no notice in the literature. Brauer<sup>12</sup> noted its occurrence in some of his patients with dermatoses; but here it was doubtless a part of the general exfoliative process, as we have shown that it may be. Harrison<sup>1</sup> states as his impression that patients on combined mercurial and arsenical treatment suffer more frequently from stomatitis than those treated with either drug alone. He feels that arsenic alone may not be so active in causing stomatitis, but adds sufficiently to the irritation produced by mercury to precipitate a stomatitis which might otherwise have failed to occur.

We have been unable to find any mention of the constitutional disturbances or of changes in the blood in this form of stomatitis. The facts that our two patients developed this phenomenon under arsenic treatment, that one had never taken mercury and the other not for two months, and that the blood picture was found to be precisely the same as that observed in our cases of exfoliative dermatitis, indicate that the stomatitis must be regarded as due to the arsenic preparation employed, in one case arsphenamin, in the other neo-arsphenamin, and that the underlying factor producing the reaction is the same as that in the exfoliative dermatitis group.

#### SIGNIFICANCE OF THE BLOOD CHANGES

The alteration of the blood picture has received little notice in the literature. Schlecht<sup>19</sup> reports two cases. The first, a patient with fatal exfoliative dermatitis after arsenophenyglycin, showed an eosinophilia of 20 per cent. (12,000 leukocytes). There was no alteration in the large mononuclear-transitional group. The second patient, with lesions of tertiary syphilis, was given four doses of salvarsan of 0.4 gm. each, combined with four intramuscular injections of from 0.02 to 0.04 gm. calomel. Ten days after the last salvarsan injection there developed a scarlatiniform rash with ulcerative stomatitis. The blood, which was

18. Leibkind, M.: Beitrag zur Kasuistik der Salvarsanexantheme (fixes exazerbierendes Erythem), Dermat. Ztschr. **31**:91, 1920.

19. Schlecht: Ueber allgemeine und lokale Eosinophilie bei ueberempfindlichkeit gegen organische Arsenpreparate, Muenchen. med. Wchnschr., No. 15, 1913.

not examined until ten days after the onset of the rash, showed leukocytosis (from 14,000 to 17,000 leukocytes), eosinophilia (from 8 to 25.5 per cent.), and an increase in the large mononuclear-transitional group (from 11 to 20.6 per cent.), with the appearance of a few myelocytes and normoblasts.

Strathy, Smith and Hannah<sup>20</sup> report fifty-eight cases of jaundice and eight cases of dermatitis as late toxic phenomena due to the arsphenamines. In most of these cases, the leukocytes varied in number from 14,000 to 34,000 per cm., and the polymorphonuclear neutrophils varied in number from 50 to 80 per cent. No further details are given.

In a recent paper Hofmann<sup>21</sup> reports a patient with exfoliative dermatitis in whom an eosinophilia of 60 per cent. was demonstrated. Eosinophilia has also been noted by Latham<sup>22</sup>, and by Stuart and Maynard.<sup>7</sup>

Attention has been drawn in a previous paper to the fact that alterations in the leukocytic picture have been recorded by various observers in poisoning from arsenic preparations other than the arsphenamins. In this connection it is of interest to note that eosinophilia has been described as an accompanying feature of mercury dermatitis by E. Hofmann<sup>23</sup>; but other changes in the blood picture are not mentioned. Bowen<sup>24</sup> describes seven fatal cases of exfoliative dermatitis of unknown etiology. In two of these patients frequent repeated examination of the blood showed no abnormalities.

Not only are references to the blood alterations few, and confined, in the main, to the mention of eosinophilia, but no author, so far as we have been able to determine, has interpreted these changes other than as due to the skin lesions. We have now observed the characteristic alteration in the blood in fourteen of sixteen cases studied; and we feel that the interpretation we have emphasized in previous papers<sup>6</sup> is justified. Briefly, the evidence allows the conclusion that arsenic has a direct action on the bone marrow, which is both toxic and stimulating. The toxic effects are seen, in mild cases, chiefly in the decrease of the polymorphonuclear neutrophil cells, which is responsible for the leukopenia. Even the presence of intercurrent infection,

20. Strathy, A. S.; Smith, C. H. V., and Hannah, B.: Report of Fifty-Eight Cases of Delayed Arsenic Poisoning Following the Administration of 606 Preparations. *Canad. M. A. J.* **10**:336, 1920.

21. Hofmann, E.: Ueber Salvarsanexantheme. *Dermat. Ztschr.* **31**:1, 1920.

22. Latham, J. D.: Exfoliative Dermatitis Due to Arsphenamin, Report of a Fatal Case. *J. A. M. A.* **73**:15 (July 5) 1919.

23. Hofmann, E.: Ueber Quecksilberdermatitis und die zugrunde liegenden histologischen Veränderung nebst Bemerkungen über die dabei beobachtete lokale und Bluteosinophilie. *Berl. klin. Wchnschr.* 1902, pp. 908, 939.

24. Bowen, J. T.: Seven Cases of Dermatitis Exfoliativa with a Fatal Ending in Five. *J. Cutan. Dis.* **28**:1 (Jan.) 1910.

which may change the leukopenia to leukocytosis, is often insufficient to cause the usual neutrophilic increase; and the leukocytosis is made up of other bone marrow cells. The stimulating effect of arsenic is apparently selective. In the mildest cases there may be eosinophilia only; if the reaction is of greater degree, neutrophilic decrease and eosinophilia. As the gravity of the damage increases, the eosinophils tend to disappear, while the remaining cells of bone marrow origin, the large mononuclear-transitional group, are increased. In maximally severe cases, all the cells of bone marrow origin disappear, leaving as the remaining leukocytic elements in the circulating blood fragile cells and lymphocytes. In two of our patients this latter phenomenon has occurred, and death has been due to aplastic anemia.

At the same time, these alterations in the bone marrow lead to a loss of the normal bodily defense against bacterial invasion. The normally phagocytic cell groups are destroyed. Various authors<sup>25</sup> have shown that when the normal function of the bone marrow is interfered with, whether by roentgen rays, benzol, or by disease (leukemia) antibody production is also decreased or completely inhibited. In our cases, while we have not specifically investigated this point, bacterial invasion of the skin or the lungs has been common, severe and usually protracted. Septicemia has been observed; and at necropsy in two cases foci of bacterial invasion without the usual cellular exudate were found in the lungs.

The blood picture, then, is not due to the accompanying skin lesion, because (1) it has been observed in cases without skin lesions; and (2) it consists of more extensive changes than simple eosinophilia. It is an essential feature of the constitutional disturbance in dermatitis and the allied reactions; it accounts for the frequency, gravity and persistence of infections in these reactions; and it may cause death by virtue of the aplastic anemia which it produces.

*The substitution of a different arsenical preparation for the one producing a reaction.*—This point has been noted in the literature, especially in the recent articles by German authors<sup>15, 17</sup> on fixed exanthems. We have found it of practical value in enabling us to continue the treatment of patients developing serious reactions early in the course of their disease. If such a procedure had not been possible, arsenic treatment must have been abandoned. Attention has been directed

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25. Hektoen, L.: The Influence of the Roentgen Ray on the Production of Antibodies, *J. Infect. Dis.* **17**:415, 1915; **22**:28, 1918; **26**:30, 1920; **27**:23, 1920.

Simonds, J. P., and Jones, H. M.: The Influence of Exposure to Roentgen Rays on the Formation of Antibodies, *J. M. Research* **33**:183, 1915; The Effect of Injections of Benzol on the Production of Antibodies, *ibid.* **33**:197, 1915.

Howell, K. M.: The Failure of Antibody Formation in Leukemia, *Arch. Int. Med.* **26**:706 (Dec.) 1920.

to the caution which should be exercised if such a substitution is attempted. The patient should be surrounded with every possible safeguard.

#### ETIOLOGY OF DERMATITIS AND ALLIED REACTIONS

We have nothing to add to the hypotheses regarding the causation of urticarial rashes. It has seemed to us that other eruptions of the mild group, such as herpes simplex and erythemas, are in all probability of infectious origin, and due to the release of organisms from latent foci of infection. We find it difficult to ascribe them directly to the toxic action of the drug.

It is with the reactions of the graver type, however, that we are particularly concerned. As yet the cause of these reactions cannot be designated accurately, but several hypotheses exist, to each of which consideration must be given. These are: (1) that dermatitis and its allied reactions are an expression of the damage to the hematopoietic system; (2) that they are due to the cumulative effect of arsenic when its normal excretion is interfered with; (3) that damage to the liver prevents the normal change of the arsenical drug from a toxic to a nontoxic form; and (4) that they are an expression of anaphylaxis.

*The hematopoietic cause of dermatitis.*—Bétances,<sup>26</sup> in an article of which only the abstract is accessible to us, states that various symptomatic skin complexes, such as dermatitis exfoliativa (Wilson-Brocq), pityriasis rubra (Hebra), chloroma, mycosis fungoides, and others, are due directly to disturbances of hemopoiesis. He bases this conclusion on histologic study of the lesions, particularly in the skin. He concludes that the pathologic process in all these diseases is the same; that it consists of a hyperplasia of the hemopoietic unity with a total or partial incapacity of the same to form differentiated myeloid or lymphoid cells, and that it is caused by certain lymphotoxins, myelotoxins or toxic lipoids acting on the hemopoietic unity. This hypothesis is of interest in view of the findings in the blood of our patients, which may perfectly simulate aleukemic lymphatic leukemia. Such a preliminary diagnosis was made in one of our cases.

*The cumulative action of arsenic.*—The fact that arsenic has been found in the excreta, particularly the urine, for long periods of time after its administration (Stuart and Maynard, ninety-seven days) has led to the assumption that, the permeability of the kidney for the drug having been impaired, arsenic gradually accumulates in the body until a toxic level is attained. Under these circumstances, perhaps, the skin takes on the function of excretion, and the irritating qualities of the

26. Bétances, L. M.: Relation Pathogenique entre les Leucémies et certaines Dermopathies, *Haematologica* 1:1 (April) 1920; abstr. in *Arch. Dermat. & Syph.* 2:655, 1920.

drug produce a dermatitis. We have not made studies of arsenic excretion in our cases. However, this hypothesis is unsatisfactory in that it fails to explain the recurrence of dermatitis when minute doses of the drug are given after an interval of months; especially in view of the fact that in some patients in whom recurrences have occurred, no kidney damage has been demonstrable in the interim between reactions.

*The question of liver damage.*—This has been particularly mentioned because of the frequency of the association of jaundice and dermatitis. The responsibility for arsenical jaundice is, as is evident from a study of the literature, hard to fix. A few writers, chief among them Milian, feel that it is always due to syphilis—a hepato-recidive. Others, the larger group, are inclined to place all the blame on arsenic. Recently Stokes, Ruedemann and Lemon<sup>27</sup> reached the conclusion that the large majority of cases of jaundice arising in the course of anti-syphilitic treatment are infectious, possibly epidemic, in type; and that in a few cases only can the blame be laid on arsenic, syphilis or underlying surgical conditions. These conclusions are in accord with our own experience; and we believe jaundice, uncomplicated by other toxic reactions, to be due to arsenic only rarely. However, it is true that a certain proportion of cases of dermatitis are complicated by jaundice, which frequently appears late in the course of the reaction.

Among the few facts known regarding the metabolism of arsphenamin in the body the chief are that it is taken up by the liver, stored there, and given out in some form presumably less toxic than its original state. It is possible that under the influence of factors not clearly understood this function of the liver may temporarily be thrown out of commission and the arsenic preparation allowed to circulate through the body unchanged. In this form it is markedly vasculotoxic, and may, therefore, so impair the smaller blood vessels as to permit its exudation into the sites of greatest damage, the skin and the bone marrow. As is shown by necropsy examinations, the liver is frequently damaged anatomically, by acute yellow atrophy, central necrosis, or marked fatty changes. On the other hand, in some cases, our own for example, no gross or microscopic damage in the liver is demonstrable; and if this hypothesis is accepted, the changes must then be assumed to be functional.

The same objections apply to this hypothetic explanation as to the inhibition of the normal excretion of arsenic with its subsequent cumulative toxic effect. It also fails to explain either recurrent dermatoses after minute doses of the drug, or, unless we assume that the various

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27. Stokes, J. H.; Ruedemann, P., and Lemon, W. S.: Epidemic Infectious Jaundice and Its Relation to the Therapy of Syphilis. Arch. Int. Med. **26**:521 (Oct.) 1920.

drugs differ in degree as to their relative toxicity, the ability of certain patients to take other arsenic preparations without the development of a recurrence.

*The anaphylactic theory of dermatitis.*—The group of maculopapular rashes, exfoliative dermatitis, fixed dermatitis, and the allied reactions (itching, stomatitis, etc.) have been regarded by many workers as possible anaphylactic phenomena. The reasons for this may be summed up as follows:

1. The extreme rarity of such reactions after the first dose of the drug. Undoubted cases have, however, been reported, in which rashes of this general type have followed the first dose. Thus, two of Houck's<sup>28</sup> four patients with scarlatiniform and maculopapular rashes developed their reactions after the first dose, as did our Cases 6 and 17 (Table 5) (maculopapular rash).

2. The tendency to recurrence of the same or a different rash after further attempts to administer the same drug. In our own series this phenomenon has occurred in six of eighteen cases of exfoliative dermatitis. The interval between treatments may be very long—eighteen months in one of our patients; a year to fourteen months in several reported cases. Furthermore, the dose of the drug producing a recurrence may be exceedingly minute, as in Zuler's<sup>29</sup> case (0.00375 gm. silver salvarsan).

3. The lack of recurrence after the substitution of a different arsenical drug. This is particularly noteworthy in our own cases, and in Fuch's cases of fixed dermatitis.

4. The blood picture. In a previous paper<sup>8</sup> attention was drawn to the similarity of the changes in the blood in these cases and in anaphylactic shock. Herrick<sup>30</sup> has produced eosinophilia experimentally in guinea-pigs by intraperitoneal injections of an aqueous extract of *Ascaris lumbricoides*. He concludes that the substance causing the eosinophilia is a protein; that previous sensitization is necessary; that if the animals are immune, the production of a blood change is impossible; and that the eosinophilia constitutes evidence of a previous sensitization.

Experimental attempts to produce anaphylaxis in cases of drug sensitization have been generally inconclusive. The work of Bruck,<sup>31</sup>

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28. Houck, W.: Ueber medikamentöse Spätexantheme nach Intravenöse salvarsan injektionen. München. med. Wchnschr. **58**:2451, 1911.

29. Zuler: Salvarsanexantheme und Neurorezidive. München. med. Wchnschr. **67**:115, 1920.

30. Herrick, W. W.: Experimental Eosinophilia with an Extract of an Animal Parasite, Its Relation to Anaphylaxis and Certain Clinical Problems, Arch. Int. Med. **11**:165 (Feb.) 1913.

31. Bruck, C.: Die Arzneiexantheme, experimentelle Untersuchungen über das Wesen. Berl. klin. Wchnschr. **42**:517, 1910.

Klausner,<sup>32</sup> Cole,<sup>33</sup> and Kyrle,<sup>34</sup> on mercury, iodoform, potassium iodid, antipyrin and copaiba is well known. All these authors found that a few of the experimental animals developed acute symptoms, which, however, were not identical with anaphylactic shock as generally accepted. Kyrle sums up the objections to regarding drug sensitization as a manifestation of anaphylaxis by calling attention to the lack of identity of acute symptoms, the difficulty of distinguishing the ordinary toxic effects of the drug, and the fact that all conceptions of anaphylaxis depend upon protein as an antigen.

Swift<sup>35</sup> sensitized nineteen guinea-pigs with a mixture of arsphenamin and guinea-pig serum. From twenty to forty-two days later he reinjected them with arsphenamin. Three of the pigs died acutely, and at necropsy showed the characteristic findings of anaphylactic shock; two had very severe, four marked, and three slight clinical symptoms of shock. Seven showed no symptoms. All controls were negative.

Hanzlik and Karsner<sup>36</sup> have reported experimental data on the acute anaphylactoid phenomena observed after the intravenous injection of various colloids and the arsphenamins. Their study was partly inspired by the tendency of many authors to regard the nitritoid crisis after arsphenamin as anaphylactic in origin. They conclude that the arsphenamins, even in very small doses, injure the circulation, giving rise to symptoms of an anaphylactoid nature; but that since the characteristic feature of anaphylactic shock, pulmonary distention, was absent, and other phenomena of acute anaphylaxis were also lacking, these disturbances should not be regarded as in the same category with true anaphylaxis or as bearing any causal relation to it whatsoever, or vice versa.

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32. Klausner, E.: *Arzneiexantheme und Ueberempfindlichkeit*, Munchen, med. Wehnschr. **57**:1983, 1910.

33. Cole, H. N.: *Drug Exanthemata in Relation to Anaphylaxis*, Cleveland M. J. **10**:422, 1911.

34. Kyrle, J.: *Zur Frage der Arzneiempfindlichkeit*, Arch. f. Dermat. u. Syph. **113**:541, 1912.

35. Swift, H. F.: *Anaphylaxis and Salvarsan*, J. A. M. A. **59**:1236 (Oct. 5) 1912.

36. Hanzlik, P. J., and Karsner, H. T.: *Anaphylactoid Phenomena from the Intravenous Administration of Various Colloids, Arsenicals and Other Agents*, J. Pharmacol. & Exper. Therap. **14**:379, 1920. *A Comparison of the Prophylactic Effects of Atropin and Epinephrin in Anaphylactic Shock and Anaphylactoid Phenomena from Various Colloids and Arsphenamin*, *ibid.* **14**:425, 1920. *Effects of Various Colloids and Other Agents Which Produce Anaphylactoid Phenomena on Bronchi of Perfused Lungs*, *ibid.* **14**:449, 1920. *Hemagglutination in Vitro by Agents Which Produce Anaphylactoid Symptoms*, *ibid.* **14**:479, 1920. Hanzlik, P. J.: *Effects of Various Colloids and Other Agents Which Produce Anaphylactoid Phenomena on Surviving Intestine and Uterus*, *ibid.* **14**:463, 1920.

In a recent paper Auer<sup>37</sup> has made an important contribution to this problem. He has been able to produce, in rabbits sensitized and reinjected with horse serum, severe inflammation of the ear, with formation of crusts and tissue destruction and sometimes dry gangrene of the ear tip, merely by the brief local application of xylol. In normal controls, in animals given only one injection of horse serum just preceding the application of xylol, and in sensitized but not reinjected rabbits, such local treatment caused only a mild inflammation with more or less edema, which disappeared in two or three days, leaving a normal ear.

Auer interprets this phenomenon as follows:

The ear lesions of the sensitized reinjected rabbits which develop after the application of xylol are interpreted as a primary anaphylactic reaction. This primary anaphylactic reaction is considered the result of a local autoinoculation of the ear tissues with circulating antigen. The local autoinoculation is brought about by the irritant action of the xylol which causes an inflammation and edema of the site of application. An anaphylactic reaction may now occur because the inflamed tissues are more active metabolically than normal tissues and therefore the inflamed cells are affected by more antigen per unit of time than the normal cells. A subliminal concentration of antigen for non-inflamed sensitized cells may thus become effective when inflamed sensitized cells are concerned.

This process may theoretically occur in any tissue of a sensitized animal which can show an anaphylactic reaction, for example the intestines, lungs, heart, skin, nerves, arteries, etc. It is possible that this interplay of conditions may explain a number of functional abnormalities in the human subject.

This work suggests an interpretation for the arsenical reactions under discussion. It may be admitted that a nonprotein substance cannot act as an antigen and that arsphenamin and other arsenicals do not, as suggested by Swift, change the nature of the serum so that it acts like a foreign protein and induces a condition of hypersensitivity. On the other hand such reactions may occur in patients who are sensitive to some protein, possibly, as suggested by Stokes,<sup>38</sup> of bacterial origin. Arsphenamin, which is a vascular toxin,<sup>39</sup> may, in the manner suggested by Auer, lower the threshold for the unknown antigen and increase vascular permeability. This in turn may cause the deposit of arsenic, normally taken up by the liver, in the structures where its toxic action is observed, notably in the bone marrow and in the skin.

37. Auer, J.: Local Autoinoculation of the Sensitized Organism with Foreign Protein as a Cause of Abnormal Reactions, *J. Exper. M.* **32**:427, 1920.

38. Stokes, J. H.: The Application and Limitations of the Arsphenamins in Therapeutics, *Arch. Dermat. & Syph.* **2**:303 (Sept.) 1920.

39. Ricker, G., and Knappe, W.: (Mikroskopische Beobachtungen am lebenden Tier über die Wirkung des 606 und 914 auf die Blutströmung, *Med. Klin.* **8**:1275, 1912) made direct microscopic observations of the capillary bed in living animals during the administration of arsphenamin and neoarsphenamin. They found that both drugs caused a slowing of the blood stream, dilatation of the capillary bed, stasis and hemorrhage.



Its action on the bone marrow produces the blood changes upon which we lay so much stress. The skin lesions may be caused by the reaction of the tissues to the locally deposited irritant.

This hypothesis disposes of some of the discrepancies noted above. It accounts for the fact that in some cases reactions occur after the first injection. It eliminates the objection raised by the impossibility of producing experimentally anaphylaxis with arsphenamin by any method heretofore tried. It opens up a new conception of the varieties of anaphylactic manifestations, and removes the objection that these patients do not show the symptoms of acute anaphylactic shock, but it still does not adequately explain the drug substitution phenomena which we have observed.

#### SUMMARY

1. We have presented a study of twenty-three cases of dermatitis and allied reactions following the use of arsenical products in the treatment of syphilis.

2. Such reactions are equally frequent in either sex, but they are about three times as liable to occur in the white race as in the colored.

3. Evidence is presented that the lesions of syphilis or the duration of the disease exercise no modifying influence upon the incidence of dermatitis. Two of our twenty-three cases occurred in patients in whom syphilis could be ruled out.

4. Dermatitis has been observed by us to follow all chemotherapeutic arsenic compounds which we have employed in the treatment of syphilis.

5. In the majority of cases in our series, arsenic was the only drug employed so that mercury and potassium iodid as causative factors can be excluded.

6. Reactions of this group tend to appear early in the course of treatment.

7. In some cases, certain prodromal symptoms may be recognized. These consist of itching, mild or fleeting macular, maculopapular, or vesicular skin eruptions, stomatitis, prolonged fever, or marked malaise. The occurrence of any of these during the use of arsenical products should lead to a suspension of treatment and a general survey of the patient.

8. Dosage, technic of administration, and impurities in the drug can be excluded as etiologic factors.

9. The lesions may be classified, on the bases of the constitutional manifestations and their importance, as mild or severe. In the mild group fall urticarial, erythematous and herpetic rashes. In the severe group are the macular, maculopapular, and exfoliative rashes, itching and stomatitis.

10. Urticaria is fairly common in association with the nitritoid crisis. The more severe constitutional manifestations are absent, and in most cases arsenical treatment may be continued. No patient so treated has later developed a more serious rash. The same may be said of herpes simplex and the erythematous rashes, except that in these cases fever and leucocytosis are frequently found.

11. The characteristics of the rashes of the severe group are described. Attention is drawn to characteristic alterations in the blood picture, which were present in fourteen of sixteen cases studied. The changes consist in general of leukopenia, decrease in polymorphonuclear neutrophiles, eosinophilia, increase of the large mononuclear-transitional group, and the appearance of many fragile cells.

12. The complications of dermatitis exfoliativa, including acute nephritis, polyneuritis, jaundice, skin infection, bronchopneumonia, and septicemia, are discussed.

13. Attention is directed to the possible relation between the complications due to infection and the disturbance of hematopoiesis.

14. The sensitiveness of the patient to the drug causing the original reaction persists over long periods of time and is made manifest by even small doses of the same drug. However, certain patients, who cannot be accurately distinguished, are able to take other less toxic arsenical drugs without the development of reactions of this type.

15. The prognosis of these reactions is grave. Among our series of twenty-three patients there have been five deaths. The pathological picture is briefly described.

16. Patients with itching without skin lesions, and with stomatitis due to arsenical preparations have been found to present a blood picture similar to that described in the exfoliative dermatitis group.

17. The literature is reviewed, and the possible etiologic factors in reactions of this group are discussed. The evidence is in favor of their anaphylactic origin.

## THE TOTAL NONPROTEIN NITROGEN CONSTITUENTS OF THE BLOOD IN ARTERIAL HYPERTENSION \*

J. Lisle Williams, M.D.

CHICAGO

Arterial hypertension is regarded frequently as a manifestation of chronic nephritis. In recent years, however, there is a growing belief that hypertension alone is not necessarily evidence of nephritis. Allbutt<sup>1</sup> was among the first to recognize from clinical observations that hypertension may be present without nephritis; this condition he termed "hyperpiesis." Under the title "primary hypertensive cardiovascular disease," Janeway<sup>2</sup> described the same disorder, while more recently Mosenthal<sup>3</sup> and others have suggested the term "benign or essential hypertension." Krehl<sup>4</sup> observed hypertension in a number of patients with other clinical symptoms not supporting the diagnosis of chronic nephritis. Gross and microscopic examination of the kidneys of one of these patients failed to reveal abnormal changes.

Until renal function was estimated by the phenolsulphonephthalein test and by the quantitative determination of the nonprotein nitrogen constituents of the blood, the evidence of the kidney disease obtained was chiefly anatomical or clinical. Mosenthal observed essential hypertension in two patients with normal blood urea and phenolsulphonephthalein excretion; the postmortem examinations revealed practically normal kidneys. Rappleye<sup>5</sup> studied the kidney function in 100 patients with hypertension. Almost 70 per cent. of these had normal phenolsulphonephthalein excretion or blood urea nitrogen values. In the remainder, the renal function so determined was impaired only slightly. Thirteen of these 100 patients died, and in ten of the eleven postmortem examinations made death was found to have been due to cardiovascular disease or to an intercurrent infection.

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\* From the Pathological Laboratory, St. Luke's Hospital; aided by the Seymour Coman Fund.

1. Allbutt, C.: *Diseases of the Arteries, Including Angina Pectoris*. London, Macmillan & Co. 1915; Arteriosclerosis and the Kidneys, *Brit. M. J.* **1**:854, 922, 1911.

2. Janeway, T. C.: A Clinical Study of Hypertensive Cardiovascular Disease, *Arch. Int. Med.* **12**:755 (Dec. 1913).

3. Mosenthal, H. O.: Essential Hypertension, *Med. Clin. N. America* **1**:101 (July) 1917.

4. Krehl, L.: *Deutsch. med. Wchnschr.* **3**:1872, 1905.

5. Rappleye, W. C.: The Kidney Function in 100 Cases of Hypertension, *Boston M. & S. J.* **179**:441, 1918.

The patients studied by Stengel<sup>6</sup> and designated by him as "arterio-  
lar fibrosis" were without functional evidence of renal disease. Many  
of them lived for several years and finally died from cardiovascular  
disease. In Meara's group<sup>7</sup> of patients with symptoms corresponding  
to the hyperpiesia of Allbutt, a few patients had a slight impairment of  
renal function, but uremia was rarely a cause of death.

Folin and Denis,<sup>8</sup> Myers, Fine and Lough,<sup>9</sup> Baumann and others<sup>10</sup>  
regard the estimation of the uric acid of the blood as the most delicate  
test for kidney efficiency. They observed many patients with "early  
interstitial nephritis" in whom the uric acid was the only nonprotein  
nitrogen substance of the blood increased. Hopkins<sup>11</sup> found that in  
climacteric hypertension kidney function is not materially affected.

That pure hypertension may be due to sodium chlorid retention in  
the blood is a conclusion reached by Allen<sup>12</sup> from observation of hyper-  
tension with clinical symptoms improved by water and salt restriction;  
the kidney function of these patients, except for the salt retention, was  
normal.

This report is primarily that of a chemical study of the nonprotein  
nitrogen constituents of the blood of patients with arterial hyperten-  
sion but with no clinical evidence of nephritis. The results of such  
determinations on the blood of fifty-five patients from the medical  
services of Drs. J. L. Miller, J. A. Capps, A. R. Elliott and R. B.  
Preble at St. Luke's Hospital, Chicago, furnish the basis of this report,  
and the patients themselves are divided into two groups, depending on  
the amount of the various nonprotein nitrogen substances in the blood  
and the alterations of the urine. Some of these patients were examined  
repeatedly over a period of from one month to two years.

The blood urea nitrogen was determined by the Van Slyke and  
Cullen<sup>13</sup> modification of the Marshall urease method. The other non-  
protein nitrogen constituents of the blood were determined according

6. Stengel, A.: The Classification of Chronic Nephritis and the Relation of  
Infection to Kidney Disease, *Med. Clin. N. America* **1**:217 (Sept.) 1917.

7. Meara, F. S.: Hyperpiesia of Clifford Allbutt, *Med. Clin. N. America*  
**2**:1 (July) 1918.

8. Folin, O., and Denis, W.: The Diagnostic Value of Uric Acid Deter-  
mination in the Blood, *Arch. Int. Med.* **16**:33 (July) 1915.

9. Myers, V. C.; Fine, M. S., and Lough, W. G.: The Significance of Uric  
Acid, Urea and Creatinin of the Blood in Nephritis, *Arch. Int. Med.* **17**:570  
(April) 1916.

10. Baumann, L.; Hansmann, G. H.; Davis, A. C., and Stevens, F. A.: The  
Uric Acid of the Blood as Compared with the Renal Dietary Test, *Arch. Int.  
Med.* **24**:70 (July) 1919.

11. Allen, F. M.: Arterial Hypertension, *J. A. M. A.* **74**:652 (March 6) 1920.

12. Hopkins, A. H.: Climacteric Hypertension, *Am. J. Med. Sc.* **157**:826,  
1919.

13. Van Slyke, D. D., and Cullen, G. E.: *J. A. M. A.* **62**:1558 (May 16) 1914.

to the recent methods of Folin and Wu.<sup>14</sup> The nonprotein nitrogen substances of the blood of many patients were estimated at repeated intervals.

#### GROUP I

In this group there are included thirty-six patients with arterial hypertension and with only slight clinical evidence of nephritis. The illness in five of these was diagnosed chronic nephritis by the attending physicians, in spite of very little change in the urine. In this group there are eleven men and twenty-five women; the age average was 54.3 years. The clinical diagnosis for five patients was hypertension alone; for five others it was chronic nephritis or cardiorenal disease; for five each it was colitis and arteriosclerosis; for four, tertiary syphilis or syphilitic myocarditis; for three each, chronic cholecystitis, cardiac decompensation and angina pectoris; for two each, cystitis, gout, diabetes, chronic arthritis and chronic myocarditis; for 1 each, cirrhosis of the liver, fibromyoma uteri and abdominal adhesions. Neither albumin nor casts were found in the urine of twenty-one patients, a trace of albumin was found in three cases, a few casts only in one case, and albumin and casts in eleven cases. Repeated examinations of the urine demonstrated the presence of albumin and casts in minimal amounts for most of the patients.

The blood urea nitrogen varied from 10.1 to 29.9 and averaged 18.9 mg. per 100 c.c.; the total nonprotein nitrogen varied from 22.4 to 59.0 and averaged 37.6 mg.; the uric acid varied from 1.8 to 6.95 and averaged 3.06 mg.; and the creatinin varied from 1.29 to 2.3 and averaged 1.7 mg. Only thirteen of these patients had a blood urea nitrogen of more than 20 mg., twenty-three had a total nonprotein nitrogen of more than 35 mg. per 100 c.c. The blood uric acid of seven of twenty-three patients was more than 3 mg. per 100 c.c.; and of three of twenty-two patients the creatinin was more than 2 mg. per 100 c.c. of blood.

The blood pressure was determined frequently and with many patients it varied markedly. The maximum systolic pressure ranged from 170 to 248 mm. of mercury, the diastolic from 70 to 160 mm. The phenolsulphonephthalein test of the kidney function of twenty-nine patients (thirty determinations) ranged from 21 to 90 per cent. for the two hour period, and averaged 53.3 per cent. For twenty-one patients the excretion was less than 60 per cent.; the urea and total nonprotein nitrogen of the blood of six of these patients were moderately increased, in fifteen cases they were normal or slightly increased. Both tests gave evidence of renal impairment in six patients. For two the blood urea

14. Folin, O., and Wu, H.: A System of Blood Analysis, *J. Biol. Chem.* **38**:81, 1919.

and total nonprotein nitrogen were normal and the 'phthalein excretion was normal or increased (90 per cent. in one patient). Excluding patients with cardiac decompensation, the two tests agreed in 75 per cent. of the cases. The blood Wassermann test for syphilis was positive in two of twenty-three patients.

Dyspnea on exertion was the most common symptom, and was present in sixteen patients. In thirteen patients the symptoms were headache; in eleven dizziness and swelling of the feet and legs; in eight each, nocturia and abdominal distress; in seven each, precordial pain and cardiac palpitation; in six each, weakness and nervousness; in five each visual disturbances or spots before the eyes, flatulence and nausea; in four each, cramps in the legs, loss of weight, anorexia, and cough; in three each, hoarseness, tinnitus aurium, constipation, and polykinuria; in two each, polyuria, dysuria, incontinence, backache, vomiting and diarrhea.

Four patients had scarlet fever in childhood; four had syphilis. In one case the hypertension was ascribed to a pregnancy seven years before. One patient had had erysipelas several years previously; another had had rheumatism, and a third had had typhoid fever. Two patients were alcohol and tobacco habitués, and one patient was intemperate in eating. The average duration of the arterial hypertension as far as could be determined was 3.2 years.

Hypertrophy of the heart, the most common alteration found in the physical examination, was observed in twenty-seven patients. The liver was enlarged in thirteen. There was a secondary mitral murmur in twelve. Sclerosis of the peripheral arteries was pronounced in nine; a dilated aorta in six; edema of the feet and legs was present in seven. Five patients had hypostasis of the lungs; four a gallop rhythm; three an alternating pulse; three a palpable kidney or kidneys, and three some degree of cyanosis. Obesity and enlarged joints each were present in four cases. In three patients the teeth were badly decayed. Two patients each had generalized edema, marked emaciation, hydrothorax and a palpable colon. Ophthalmoscopic examination of the eye grounds of eight patients was negative in four, but revealed sclerosis of the retinal vessels in two, arteriovenous compression in one case, and a low grade retinitis in another.

There was no relation between the height of the blood pressure and the amount of any of the nitrogenous waste substances found in the blood. Two patients—one with the highest, the other with the lowest blood pressure—had nitrogen values that differed only slightly. The patients having dyspnea with cardiac decompensation had the highest values for nonprotein nitrogen of the blood of the group. In these patients the slight nitrogen retention could be accounted for by the

passive hyperemia of the kidneys. No relationship could be established between any of the other symptoms or physical findings and the amount of nitrogen in the blood.

Of the thirty-six patients, thirty-one are known to be living for as long as from two months to two years, and of these eighteen are improved, twelve are as before, and two are worse. The condition of three patients is unknown, and two are dead. Both died of cardiac failure, this diagnosis for one being confirmed by a postmortem examination. Among the changes observed during this examination were hypertrophy and dilatation of the heart, passive hyperemia of the liver and kidneys, and moderate sclerosis of the aorta and larger arteries. In the kidneys a few scattered hyalinized glomeruli were found, such as are present in the kidneys of any person at that age dying of a disease unrelated with arterial hypertension.

#### GROUP II

The symptoms of the disease in the patients of this group differed very little from those in Group I, but in the urine there were larger quantities of albumin and more casts, whereas the blood contained more of the nitrogenous waste products, particularly uric acid. There are nineteen patients in this group, thirteen men and six women, varying in age from 40 to 69 and averaging 58.2 years of age. The clinical diagnosis in six cases was chronic nephritis or cardiorenal disease; in two each, tertiary syphilis, angina pectoris, arteriosclerosis, diabetes and hypertension alone; and in one each, abdominal adhesions, cardiac decompensation, chronic cholecystitis and cerebral hemorrhage. The urine of four patients contained neither albumin nor casts, of three, only albumin, of one, hyalin casts, and of ten both albumin and casts. The blood urea nitrogen varied from 11.4 to 32.7 mg. and averaged 21.5 mg. per 100 c.c., the total nonprotein nitrogen from 28.1 to 56.4 and averaged 42.9 mg.; the uric acid from 2.48 to 9.02 and averaged 5.39 gm., and the creatinin from 1.49 to 2.24 and averaged 1.80 mg. The urea nitrogen of the blood of ten patients was more than 20 mg. per 100 c.c. and of thirteen the total nonprotein nitrogen was more than 35 mg. The uric acid of the blood of twelve patients in this group was more than 3 mg. per 100 c.c., and the creatinin content for four of ten patients was more than 2 mg. per 100 c.c. As has been stated in Group I, the higher values for nitrogen retention are associated with the symptoms of cardiac insufficiency, dyspnea, edema of the feet and legs, nocturia and precordial pain.

The systolic blood pressure ranged from 160 to 268 mm.; the diastolic from 72 to 160. The phenolsulphonphthalein excretion in two hours for fifteen patients varied from 30 to 74.3 per cent. and

averaged 47.2 per cent. Nocturia was the most common symptom observed in nine cases, headache and dyspnea each in six; cough, dizziness, and abdominal distress each in four; blurred vision, polyuria, weakness, nervousness, nausea and vomiting each in three; tinnitus, cardiac palpitation, polykinuria, backache, insomnia, precordial pain, and loss of weight each in two. One patient (Wassermann negative) reported a previous syphilitic infection, another reported an attack of scarlet fever in his youth, and a third excessive alcoholism.

Hypertrophy of the heart as in the patients of the first group was common (fifteen of the nineteen patients); in eight cases the liver was enlarged; in five there was a regurgitant mitral systolic murmur; in four, pulmonary hypostasis and sclerosis of the peripheral arteries; in three each, a gallop rhythm, cyanosis and marked edema of the extremities; in two each, an alternating pulse, hydrothorax, a dilated aorta and a regurgitant aortic murmur; and in one each, marked ascites and hypertrophy of the prostate gland.

Twelve of the nineteen patients in Group 2 are living for from two to twenty months; five are dead, and the condition of two is unknown. Five of the living are improved, and the clinical symptoms of seven are unchanged. The cause of death of two patients was cerebral hemorrhage. One patient died of angina pectoris, one of diabetic coma, and one of cardiac decompensation. The last mentioned clinical diagnosis was confirmed by postmortem examination, and the chief anatomic changes noted were hypertrophy and dilation of the heart, senile sclerosis and fatty changes of the lining of the aorta and larger arteries, and marked passive hyperemia and healed infarcts of the kidneys. Microscopic examination of the kidney tissue disclosed no striking changes.

#### DISCUSSION

On comparing the averages of the various nonprotein nitrogen constituents of the blood in the two groups, the urea and nonprotein nitrogen are each a few milligrams higher in Group 2 than in Group 1. The uric acid averages of Group 2 are almost double those of Group 1, 5.39 mg. as compared with 3.03. The creatinin is almost the same in both groups.

The uric acid of the blood was increased in 54 per cent. of the patients of both groups; the total nonprotein nitrogen was slightly increased in 65 per cent.; and the urea was slightly increased in 42 per cent.

The phenolsulphonephthalein excretion for two hours was slightly more for the patients in Group 1 than for those in Group 2. The average phenolsulphonephthalein excretion of both groups is a trifle lower than the minimum normal value for two hours, but included in



the averages are some patients with cardiac decompensation and it is well known that this materially diminishes the amount of dye excreted. The extreme passive hyperemia of the kidneys in such patients may explain the slight increase of the non-protein nitrogen substances in the blood where anatomically there is no nephritis.

Of the prominent symptoms of the two groups, dyspnea is most common in Group 1, while nocturnal polyuria occurred twice as frequently in Group 2 as in Group 1. Edema of the feet and legs was present in 31 per cent. of the patients of Group 1, and in 16 per cent. of those in Group 2. Polyuria troubled 16 per cent. of the patients in Group 2, but only 6 per cent. in Group 1. Precordial pain and palpitation occurred almost twice as frequently in Group 1 as in Group 2. The other common symptoms, headache, dizziness, abdominal distress, nervousness, visual disturbances, nausea and vomiting were of almost the same frequency in both groups.

The changes in the urine differ slightly in that the patients of Group 2 had more evidence of renal impairment as shown by the presence of albumin and casts in the urine. Four patients of this group, however, had no albuminuria or cylindruria.

In Group 1, there is a large majority of women while in Group 2 the men largely predominate. The ages in Group 2 average slightly more than those in Group 1. In Group 2 a higher percentage of patients was diagnosed clinically as chronic nephritis, but other than this there is no striking disparity in the diagnoses.

#### CONCLUSIONS

1. There is a disease, arterial hypertension, which when uncomplicated by nephritis or cardiac decompensation gives no functional evidence of kidney insufficiency.

2. Cardiac decompensation with marked passive hyperemia of the kidneys is associated with a moderate retention of nonprotein nitrogen in the blood.

3. The height of the blood pressure bears no relationship to the amount of the nonprotein nitrogen substances in the blood.

4. Arterial hypertension with normal nonprotein nitrogen values in the blood and normal kidney excretion, determined by functional tests and urine examinations, does not justify the clinical diagnosis of chronic nephritis.

I wish to thank Drs. E. F. Hirsch and E. R. LeCount for valuable suggestions in preparing the manuscript, and Drs. J. L. Miller, J. A. Capps, A. R. Elliott, and R. E. Preble for opportunity to study their patients.

## Book Reviews

THE DISEASES OF INFANTS AND CHILDREN By J. P. CROZER GRIFFITH, M.D., PH.D., Professor of Pediatrics in the University of Pennsylvania. Two octavo volumes totaling 1542 pages, with 436 illustrations, including 20 plates in colors. Philadelphia and London: W. B. Saunders Company, 1919. Cloth, \$16.00 net.

Dr. Griffith's little book on "The Care of the Baby" has been for more than a quarter of a century the trustworthy guide not only to young mothers but to young physicians. With that great success and the author's many sound contributions to pediatric literature, it seemed strange that he did not long ago write a textbook. The explanation is to be found in these two handsome and well printed volumes. They form a small, but unusually complete encyclopedia on pediatrics, and include surgical as well as medical topics. Part of Volume I and all of Volume II are devoted to diseases of organs. The whole work exhibits an unusually rich pediatric experience, well arranged by a trained and broadly cultivated mind. An extensive reading of the literature is shown in connection with almost every topic, and the reader is assisted in personal study by numerous references to the original sources. In many cases these are brought up to about the time of the war, and one can assume that the author, like so many others, had his working plans deranged by that event. If the reader misses references to important articles since about 1916, he is fortunate in having available a key to the most important work up to that time. The usual chapters on anatomy and physiology of early life, hygiene, breast feeding and other details of food, proprietary foods, diet in health and disease are given almost 200 pages. They are sound, practical and unusually detailed, and so well arranged that it is easy to find information on any of the subjects with the minimum trouble. Equally good are the chapters on general methods of examination and diagnosis, and morbidity and mortality. The chapter on therapeutics of infancy and childhood shows the experienced hand and brain. Diseases are described after a natural classification, beginning with those of the new-born. Then follow the infectious diseases, the definition of which does not show the author's usual care for verbal accuracy. Thus, it is difficult to understand why he says, "pneumonia *appears to be* (*italics ours*) quite certainly an infectious disorder," although no objection can be made to classifying pneumonia, as well as rheumatism and chorea in other groups. Contact carriers and droplet dissemination are well described.

The sections on the eruptive fevers bring out the author's mastery of clinical details and his skill in description. In the diagnosis of smallpox, however, he does not take advantage of any of the recent biologic methods, which certainly deserve extensive trials. In very few places can one object to the matter, but some items may be mentioned. The reviewer believes it not only unnecessary but harmful to cleanse the skin "vigorously" before vaccination, except in exceedingly dirty children. He also thinks the cross scarification recommended is bad. Army surgeons during the war put the quietus on that antiquated and incendiary method, which is largely responsible for much of the objection to vaccination among physicians and laymen. There is no reference to the interesting relations of chickenpox and zoster, nor is the importance of pemphigus set forth with deserved emphasis. In cerebrospinal fever, the varieties of organisms and their bearing on treatment are not utilized as they should be. In diphtheria the matter is more nearly up to date. The treatment of malaria should not be ended as the author says, by giving small doses of quinin for two or three weeks, but continued prophylactic treatment should be carried out for months, in order to prevent the child from becoming

a carrier, with or without symptoms, the latter often misunderstood. Poliomyelitis is well described, but nonsuppurative encephalitis deserves more space than it gets in the second volume, without sufficient reference to the possible confusion with poliomyelitis under that rubric. The pathology and early clinical features of tuberculosis do not sufficiently reflect the valuable studies of recent years, including the significant researches of Opie on tuberculosis of lymphatic tissues. Syphilis is well cared for. General and nutritional diseases are well described, though it is strange not to find some reference to the results of the war and the blockade on rickets and some other diseases. The author's reason for classing rheumatism among general and constitutional diseases, because the causative germ is not known, will strike many as rather feeble. Progress in the investigation of infectious diseases would have been much slower than it was if that view had been held widely. Leaving out all references after 1914, and some useful ones before that, makes this section less impressive than it should be. Focal infection certainly deserves some discussion here. The section on diabetes insipidus has no reference later than 1892 and is quite out of line with current ideas. The chapter on pellagra, like some others, shows by failure to mention vitamins the stimulus that word gave to the study of nutrition and its alterations. The other diseases are arranged by organs, and the text shows the same command of the subject. The placing of the pneumonias, with "inflammation of the lungs" as a subhead, forces one to realize the great value of anatomic classification, as well as the loss incurred by making the etiologic viewpoint secondary. The author's presentation of pneumonia, however, is most commendable. He shows how the titles "lobar" and "lobular" are misleading, that "catarrhal" does not fully express the pathologic changes which occur; he describes well the clinical features. More details on the etiology and etiologic diagnosis could have been added with advantage, but the young reader should have these and the older one would probably need a younger head to assist him in that part of the work. The choice of "eczema" to the now familiar dermatitis is another relic of the past.

These few examples only emphasize the immense amount of sound information the author has given. Though not up to date as regards scientific effort, it does distinct credit to the specialty of pediatrics and may serve as a baseline to indicate future advance, just as it can be used to show the advance from the eras of J. Lewis Smith or Meigs and Pepper. It is, in fact, a book to refer to and to use. The illustrations are numerous, often original and well chosen. The printers' work is so well done that the spelling "pomegranite" on p. 827 almost seems as if it must be correct.

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